I. ELECTROPHILIC AROMATIC SUBSTITUTION OF METALLOCENES

II. STEREOCHEMISTRY OF HALOGEN ADDITION TO 4-t-BUTYLCYCLOHEXENE

III. LITHIUM ALUMINUM HYDRIDE REDUCTION OF CIS-2,6-DIMETHYLCYCLOHEXANONE

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ABSTRACT

PART I.

The mechanism of electrophilic substitution of metallocenes was investigated by the competitive acetylation of ferrocene and ruthenocene and of ferrocene and 1,1'-diethylferrocene. Solvolyses of ω-ferrocenylalkyl p-bromobenzenesulfonates did not show any significant aryl participation. These results lead to the hypothesis that direct interaction between the metal and the electrophile is of great importance in electrophilic substitution reactions of metallocenes.

PART II.

The bromination and chlorination of 4-t-butylcyclohexene have been shown to produce diequatorial dihalides as well as diaxial dihalides. The amount of diequatorial dichloride produced increases with solvent polarity. The results are explained in terms of two competing mechanisms, the classical, planar trans-addition and a carbonium ion process which increases in importance in the more polar solvents.

PART III.

Lithium aluminum hydride reduction of cis-2,6-dimethylcyclohexanone gave only 14% of the 2(e),6(e)-dimethyl-1(e)-cyclohexanol. This is in striking contrast to other results for lithium aluminum hydride reductions. Two equatorial groups adjacent to a reaction center on a cyclohexane ring thus cause an especially severe steric hindrance at that center.

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I.

ELECTROPHILIC AROMATIC SUBSTITUTION OF METALLOCENES

1. INTRODUCTION

Since the initial discovery of the aromatic behavior of ferrocene (1), it has become increasingly apparent that the metallocenes of the group VIII metals exhibit striking aromatic character. Cyclopentadienyl manganese tricarbonyl also has aromatic character since it may be acetylated, benzoylated, alkylated, sulfonated, and metalated (2,3,4). The heats of formation of ferrocene and nickelocene indicate a high resonance stabilization of the metallocene system although nickelocene is considerably less stable than ferrocene (5,6). The aromatic stability of ferrocene is further exemplified by its failure to form an adduct with maleic anhydride (1). Also, ferrocene is not hydrogenated in the presence of platinum catalyst (1). Ferrocene has been shown to undergo Friedel-Crafts alkylations (7) and acylations (1,8), metalations (9,10,11), and sulfonations (12), usually with remarkable ease. Nitration and direct halogenation of ferrocene have been unsuccessful largely because of the sensitivity of ferrocene to the oxidizing conditions of these reactions and the resulting decomposition of the organometallic compound (1,13,14).

Other evidence for the high reactivity of the metallocenes comes from an examination of the conditions required to obtain electrophilic substitution. Ferrocene can be acylated in the Friedel-Crafts manner under very mild conditions (9,12,15,16). Catalysts which have been used to bring about acylation of ferrocene are aluminum chloride (1), stannic chloride (9,17), hydrogen fluoride (12), boron trifluoride (15,18), phosphoric acid (16,19,20), and trifluoroacetic anhydride (19). Reaction times are usually short; ten to sixty minutes generally suffice to complete the reaction.

A similar ease of acylation is found among the reactions of heterocyclic compounds. For example, 1,2-dimethylindole is acetylated by acetic anhydride at 100° without a catalyst (21). In a manner similar to ferrocene (16), thiophene reacts with acetic anhydride in the presence of 85% phosphoric acid (22). Stannic chloride also catalyzes the reaction of thiophene with acid chlorides in benzene solution (23).

The acylation products of the metallocenes further imply high metallocene reactivity. With acetyl chloride and aluminum chloride ferrocene gives small amounts of 1,2-diacetylferrocene (24,25,26) whereas benzene gives only monosubstitution (27). Also, both ferrocene and ruthenocene give 1,1'-diacylated products (1,28,29).

Competitive Friedel-Crafts acetylations of ferrocene and anisole, phenol, or benzene, respectively, give only acetylferrocene and no acetophenones (18). However, in these experiments not all of the reactants were accounted for.

Ferrocene may be mercurated to give disubstituted product (9,11). Various heterocyclic compounds of high reactivity are also easily mercurated (30). For example, all four hydrogens of thiophene may be substituted by refluxing in acetic acid with mercuric acetate (31). Although toluene and benzene are also mercurated at reasonable rates, the reaction requires acid catalysis and, furthermore, monosubstitution predominates (32).

Two additional electrophilic substitutions which reflect the high reactivity of metallocenes are formylation (16,18,33,34,35,36,37,38,39) and aminomethylation (Mannich reaction). Thus, ferrocene reacts with N-methylformanilide and phosphorus oxychloride to give about 70% of ferrocenecarboxaldehyde (16,33,34). Some ferrocene is often recovered unreacted. Only the more reactive aromatic hydrocarbons behave in this manner (33); for example, anthracene gives excellent yields of the 9-aldehyde (40). Again, heterocyclic aromatic compounds are similarly reactive. Treatment of indole with N-methylformanilide and phosphorus oxychloride gives 54% of 3-indolecarboxaldehyde (41).

The reaction of ferrocene with methylenebisdimethylamine and phosphoric acid in acetic acid on a water bath for ten hours gives a quantitative yield of dimethyl (ferrocenylmethyl) amine (38). From methylenebispiperidine a 70% yield of piperidinomethylferrocene is obtained (38). Reaction times required for aminomethylation of ferrocene are generally longer than those required for acylation. For comparison with heterocyclic chemistry, the aminomethylation of indole gives 40% of gramine (42). The reaction is completed more rapidly than in the case of ferrocene.

Ferrocene is sufficiently reactive so that disubstitution may occur in aminomethylation. Thus, although reaction of ferrocene with N-methylformanilide and phosphorus oxychloride cannot be made to give the dialdehyde (33), 19% of disubstituted product has been obtained from the reaction of methylferrocene with methylenebisdimethylamine, formaldehyde, and phosphoric acid in acetic acid at 90° for seven hours (39).

A pinacol rearrangement in which an aryl group migrates may be considered to be an electrophilic aromatic substitution since the migration of an aryl group involves release of electrons from the aryl group to the carbonium ion center. The extent to which a particular aryl group migrates may be expected to parallel the reactivity of that aryl group towards electrophilic aromatic substitution. Thus, 1,2-diphenyl-1,2-diferrocenylethanediol undergoes a facile pinacol rearrangement in which the ferrocene nucleus migrates (43). This result implies the greater reactivity of ferrocene compared to benzene in electrophilic substitutions.

Similarly, aryl participation in the ionization of alkyl side chain esters is an electrophilic aromatic substitution (44). In this connection the solvolysis of 2-ferrocenylethyl tosylate in 80% acetone-water proceeds 537 times faster than the phenyl derivative (45). Although other data for the solvolysis of 2-arylethyl tosylates in 80% acetone-water are lacking, from the available results for 2-phenylethyl and 2-anisylethyl tosylates in ethanol, acetic acid, and formic acid (46) a modicum of aryl participation would be expected for 2-phenylethyl tosylate in 80% acetone-water, a solvent of medium ionizing strength (47), whereas the anisyl derivatives and similarly reactive compounds would exhibit rate enhancements due to aryl participation. It is difficult to predict whether the 2-anisylethyl tosylate would solvolyze as fast as 2-ferrocenylethyl tosylate since for the 2-arylethyl system the plot of log k against <u>Y</u> is not a straight line and enough points are not available to determine the curvature.

Reactions other than the electrophilic substitutions previously discussed provide further evidence of the high reactivity of metallocenes. An adjacent metallocene nucleus greatly stabilizes a cation. For example, ferrocenecarboxaldehyde is soluble in aqueous acid apparently due to protonation to give a hydroxycarbonium ion (18). Even more conclusive is the observation that metallocenylcarbinylcarbonium ions formed on hydrolysis of the corresponding acetates are of stability comparable to the triphenylmethylcarbonium ion (45,48,49).

The central metal atom may be directly involved in the reactions of metallocenes (45,48,49). Nuclear magnetic resonance studies have shown that the metallocenes are protonated on the metal (50). Electrophilic attack may involve cites of high electron density in the metal atom. Treatments of the electronic structure of the metallocenes give more precise locations to the metal electron densities (51-57). The Moffitt treatment (51) indicates the presence of an equatorial belt of electrons around the metal consisting of the hybrid ha_g orbital and the original d_{xy} and $d_{x^2-y^2}$ orbitals of the metal. Other treatments imply that some of these electrons are tied up with bonding to the carbocyclic rings (56) although to do so would place these electrons in strongly antibonding ring orbitals. However, the ha_g orbital remains free and is expected to be well suited to release its electrons to an electrophile.

The present work comprises an attempt to further understand the electrophilic substitution of metallocenes and to quantify their reactivity. Also, several interesting results regarding metallocene reactivity were uncovered.

2. RESULTS

2.1 Competitive Acetylations

A competitive acetylation of equimolar amounts of ferrocene and ruthenocene was carried out in methylene chloride solution using boron trifluoride catalyst. One equivalent of acetic anhydride was used per equivalent of ferrocene. The separation of ferrocene, ruthenocene, and acetylated products was easily and cleanly accomplished by chromatography on alumina. Acetylferrocene was isolated in 80.5% yield (based on ferrocene) and 84% of the ruthenocene was recovered unreacted. A very minute amount of diacetylferrocene was also obtained. If any unreacted ferrocene was present, at most there would have been traces only. Under the conditions of this acetylation it was shown in a separate run that ruthenocene gives good yields (80-90%) of monoacetylruthenocene, but no diacetylruthenocene is formed (28,29). Identification of the products was accomplished by melting point determination and ultraviolet spectra. About equal quantities of ferrocene and ruthenocene remain unaccounted for and may have been lost through decomposition during reaction. Some operational losses may be expected, too. Aqueous layers obtained during the work-up were colored blue due to the presence of ferricinium ion. This acetylation method is known to give 88-90% yields of acetylferrocene, no other material being obtained (15).

Ferrocene and 1,1'-diethylferrocene were similarly acetylated competitively. Chromatography on alumina gave 38% of acetylferrocene and 56% of acetylated 1,1'-diethylferrocene. Again about 20% of the reactants was lost in decomposition. The ratio of 3-acetyl-1,1'-diethylferrocene to 2-acetyl-1,1'-diethylferrocene was found to be 2 by chromatographic separation of the isomers. The two isomers are individually distinguishable by ultraviolet spectra (58) although mixtures of isomers cannot be analyzed by ultraviolet spectroscopy since the absorption maxima are separated by only 4μm .

It was assumed in calculating relative rate ratios that the rate of Friedel-Crafts acetylation may be expressed by equation 1.

$$-\frac{d\,[\mathrm{Met}]}{dt} = k\,[\mathrm{Met}] \cdot \cdot \cdot \qquad (1)$$

where [Met] is the concentration of the metallocene. For competitive acetylations of two different metallocenes, the rate constant ratio will be given by equation 2.

$$\frac{k_1}{k_2} = \log \frac{[\mathrm{Met}_1]_{\mathrm{final}}}{[\mathrm{Met}_1]_{\mathrm{initial}}} \Big/ \log \frac{[\mathrm{Met}_2]_{\mathrm{final}}}{[\mathrm{Met}_2]_{\mathrm{initial}}} \qquad (2)$$

The assumption that the ruthenocene not accounted for is acetylated gives a lower limit for the rate ratio of ferrocene to ruthenocene. From equation 2 it is calculated that ferrocene is at least 10.5 times more reactive than ruthenocene towards electrophilic acetylation.

In 1,1'-diethylferrocene there are two chemically different types of positions where substitution can occur; the α-positions and the β-positions (fig. 1). Consideration of the statistical factors for substitutions at various positions compared to a single position in ferrocene gives equation 3.

$$R = \frac{2\ k_{\alpha} + 2\ k_{\beta}}{5\ k_{fer}} \qquad (3)$$

In equation 3 the constants k_{α} and k_{β} are the partial rate constants for substitution at a single α- and β-position, respectively, and k_{fer} is the partial rate constant for a single position in ferrocene. The rate constant ratio, R, is calculated from equation 2 using the amount of acetylferrocene and the total amount of acetylated diethylferrocene obtained to estimate the final concentrations of ferrocene and 1,1'-diethylferrocene. The experimental results together with an application of equation 2 lead to a value for R of 1.7. Since k_{β}/k_{α} was experimentally determined as equal to 2, partial rate factors for the α- and β-positions of 1,1'-diethylferrocene are calculated to be 1.4 and 2.8, respectively, relative to a single position in ferrocene.

2.2 Acid Strengths

It was thought that ferrocene might act as a base toward strong acids. An attempt to titrate ferrocene in

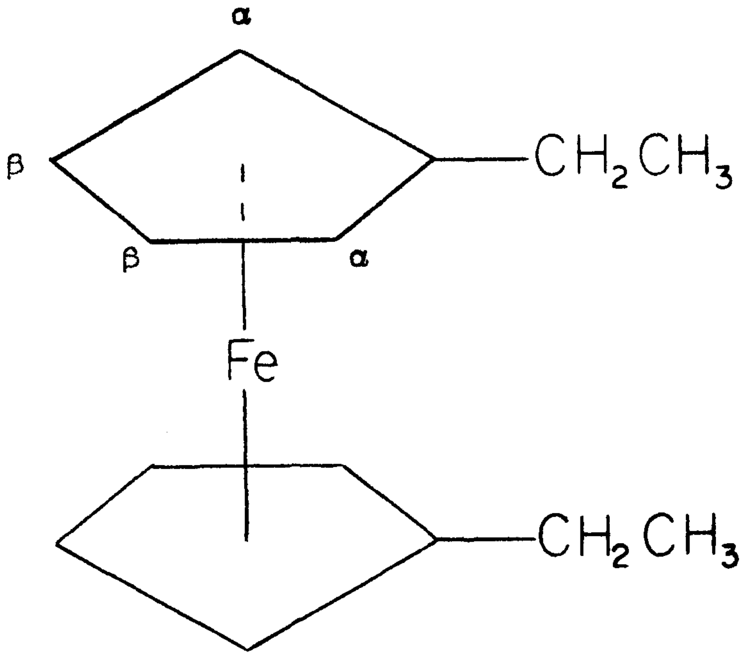


Figure 1.

acetic acid with p-toluenesulfonic acid was unsuccessful, an observation which implies that acetic acid is a stronger base than ferrocene.

Any unusual polar effects in the metallocene system would be expected to show up in the dissociation constants of ferrocene carboxylic acids. Table I lists the results of a study of dissociation constants of ferrocenecarboxylic, various ω-ferrocenylalkanoic, 3-ferrocenoylpropionic, benzoic, and phenylacetic acids in ethanol-water solvent of density 0.8916 g/cm^3 at 25°.

TABLE I

pK_A's of Acids in Ethanol-Water

Acid	pK_A
$C_{10}H_9FeCOOH$	6.61
$C_{10}H_9FeCH_2COOH$	6.4
$C_{10}H_9Fe(CH_2)_2COOH$	6.53
$C_{10}H_9Fe(CH_2)_3COOH$	6.63
$C_{10}H_9FeCO(CH_2)_2COOH$	6.33
C_6H_5COOH	6.13
$C_6H_5CH_2COOH$	6.08

2.3 Solvolysis of ω-Ferrocenyl-1-alkyl p-Bromobenzenesulfonates

Aryl participation is a form of electrophilic substitution (see the discussion in the Introduction). To further elucidate the aromatic reactivity of the metallocenes the solvolyses of some ferrocenyl side chain esters were studied. Table II lists results of the acetolysis. at 103.8° of ω-ferrocenylalkyl p-bromobenzenesulfonates. Also, values for ω-phenylalkyl and ω-methoxyphenylalkyl p-bromobenzenesulfonates extrapolated from the data of Heck and Winstein (59) to 103.8° are included. The rate constants were obtained by a least squares treatment of the data from each run. Rates were followed to about 50% completion by potentiometric titration of acid liberated and were first order as far as followed except in those cases where oxidative decomposition of the reactant became severe. It was not possible to follow the acetolysis rates to completion since oxidation of the starting materials and products became excessive at 50% completion. Acid liberated in the solvolysis appears to be consumed in the oxidation reaction. Oxidation was not prevented by ascorbic acid nor by other antioxidants but was reduced by maintaining a slow stream of oxygen-free nitrogen (60) through the solvolysis solution. Table II also contains results for the acetolysis of isopropyl p-toluenesulfonate, which provides a test of the solvolysis and titration method. A slight drift towards increasing rate was noted in the solvolyses of isopropyl p-toluenesulfonate which is probably due to a salt effect.

TABLE II

Acetolysis Rates of ω-Arylalkyl Brosylates at 103.8°

Brosylate	Conc., M	% complete	$k \times 10^5$ sec^{-1}
3-ferrocenyl-1-propyl	0.03256	27	1.52
4-ferrocenyl-1-butyl	0.02130	66	3.08
	0.02794	66	2.10
	0.02794	66	2.21
	0.04166	22	2.65
	0.02928	72	1.66
			2.34±0.54[a]
	0.0387	61	2.43[b]
5-ferrocenyl-1-pentyl	0.04036	19	2.41
	0.02291	47	2.39
			2.40±0.01[c]
isopropyl tosylate	0.2085	81	4.04[d]
	0.2080	97	3.99[d]
	0.02907	73	3.90[d]
	0.04373	97	62.4
			3.98±0.07[e]
3-phenyl-1-propyl			1.45[f]
4-phenyl-1-butyl			2.26[f]
5-phenyl-1-pentyl			2.31[f]
4-(*p*-methoxyphenyl)-1-butyl			3.04[f]
4-(2,4-dimethoxyphenyl)-1-butyl			10.8[f]

a. Average of five runs; error reported as standard deviation. b. Acetolysis at 105.4°. c. Average of two runs. d. Acetolysis at 76.0°±0.02°. Initial rates are given; least squares treatment of all points gives 4.3×10^{-5} sec^{-1}. e. Average of three runs. f. Extrapolated from data of Heck and Winstein (59).

Product studies of the acetolysis of 4-ferrocenyl-1-butyl p-bromobenzenesulfonate were performed. Although extensive oxidation occurred only 4-ferrocenyl-1-butyl acetate was obtained which was identified by infrared spectroscopy and comparison with an authentic sample. However, in one case a small amount of a non-polar ferrocene derivative was isolated by chromatography on alumina. The infrared spectrum of this substance differed from that of the expected hydrocarbon, 1,2-tetramethyleneferrocene (61), and also was not identical to n-butylferrocene (authentic samples of both hydrocarbons were prepared for comparison). The infrared and ultraviolet spectra indicated the absence of functional groups either conjugated with or separated from the ring system. Due to the small amount of material initially obtained further characterization and indentification was not possible. Another attempt to isolate this substance failed to yield any non-polar substance on chromatography on alumina.

From the acetolysis of 5-ferrocenyl-1-pentyl p-bromobenzenesulfonate only acetate ester was obtained. No product study was made of the acetolysis of 3-ferrocenyl-1-propyl p-bromozenenesulfonate.

Late in this study it was found the hydrolysis in "80%" acetone-water although slow at 50° proceeded without oxidation. Rates were first order, and the tedious potentiometric titration procedure could be eliminated since the acid liberated could be titrated to an indicator end point. Since no results for 4-phenyl-1-butyl p-bromobenzenesulfonate have been reported for this solvent, 4-ferrocenyl-1-butyl and 4-phenyl-1-butyl p-bromobrosylates were solvolyzed simultaneously to 50% completion. The results are given in Table III. No rate enhancement was observed for the ferrocene derivative which, in fact, hydrolyzed somewhat slower than the phenyl derivative.

TABLE III

Hydrolysis of 4-Arylbutyl Brosylates in
80% Acetone at 50°

Aryl group	Conc., M	% Completion	$k \times 10^6$, sec^{-1}
ferrocenyl	0.00527	50	2.49
phenyl	0.01137	61	3.15

3. DISCUSSION

3.1 Energetics of Electrophilic Metallocenyl Substitution

A simple molecular orbital calculation suggests an explanation for the high reactivity of metallocenes. The unperturbed rings are approximated by cyclopentadienyl radicals and the ring in the transition state for substitution is approximated by a cis-butadiene cation. The π-electron energy in the unperturbed ring is 5.854 β while the corresponding energy of the substituted ring is $3.854\ \beta$. There is a loss in total π-electron energy on going from the ground state to transition state of 2β; however, there is no loss of delocalization energy! The corresponding change for benzene involves a loss of total π-electron energy 2.54β and a loss of delocalization energy of 0.54β. This comparison may help explain the extreme reactivity of metallocenes.

Certain expectations derived from first principles regarding possible intermediates and mechanisms of metallocenyl electrophilic substitution may be discussed although the lack of adequate evidence does not permit any but a tentative choice of mechanism at this time.

An attacking electrophile eventually bonds to one of the carbon atoms of the carbocyclic rings displacing a hydrogen. Such an attacking species might be considered to approach the aromatic system from either side of the plane of the ring undergoing substitution. At large carbon-electrophile (C-E) distances Coulombic interaction is the predominant bonding force. No specific point of attack is discernible, and the relative energies of the different metallocene-electrophile systems as a function of the central metal atom of the metallocene is solely dependent upon differing polarizabilities. However, at short C-E distances covalent forces, London forces, and steric repulsions become important. Furthermore, specific sites of bonding are a direct result of the above forces, and initial bonding may be to one or both rings and/or to the metal.

Best covalent bonding between the electrophile and a ring will be achieved when maximum overlap with the ring π-orbital occurs. This requires that the attacking electrophile come in with orientations which are reasonably perpendicular to the rings. Extensive bonding may, of course, drastically distort the orbital geometry. If the essential features of initial attack are preserved in the intermediate stages of the reaction, two intermediate configurations are possible, which are depicted in figures 2 and 3. In figure 2 the electrophile is opposite to the ring not undergoing attack (the bottom ring) and in figure 3 it is adjacent to this ring.

A bulky electrophile allows the possibilities of steric interactions. The structure represented in figure 3 has the electrophile positioned in the central region of the metallocene system which region is more subject to steric restrictions than the more external region occupied by the electrophile in figure 2. The source of these steric restrictions stems from the steric interaction of a bulky electrophile with the central metal atom and the carbocyclic ring not undergoing substitution. Any steric hindrance will be further aggravated if orthogonal approach is to be maintained since for a given C-E distance the distances between

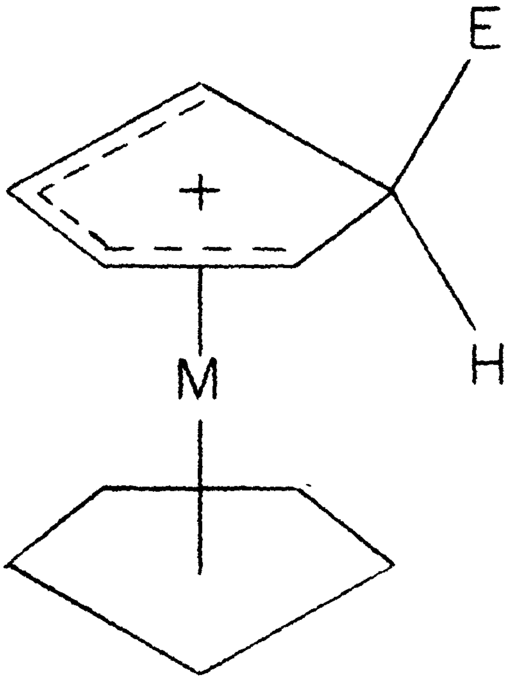


Figure 2.

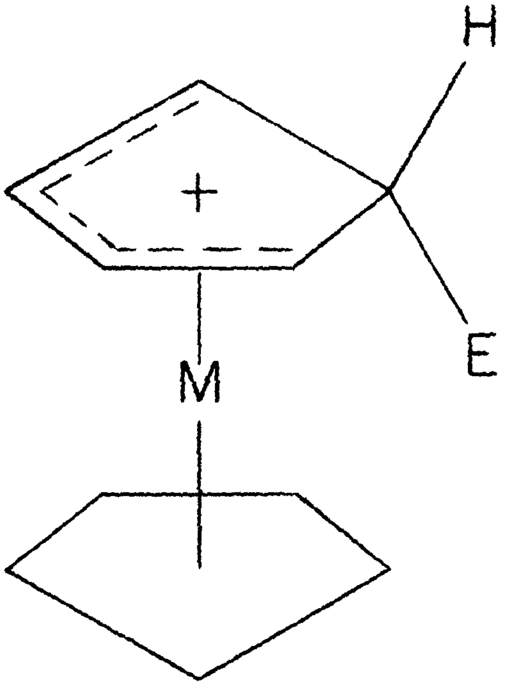


Figure 3.

the sterically interacting groups is reduced as the angle between the C-E bond and the axial direction approaches 0°. Conversely, steric interactions may be relieved by a bending away of the C-E bond from the axial direction of the metallocene system.

In contrast to the above ideas concerning a bulky electrophile, for small and unencumbered electrophiles the structure represented by figure 3 may be the more energetically favored since an especially stable intermediate may be formed if the electrophile bridges the two rings as shown in figure 4. Bonding of the electrophile occurs with both the metal-ring bonding orbitals and, as depicted by the arrow in figure 4, may also involve the electrons of the equatorial metal orbitals, ha_g and $d_{\pm 2}$ (51). Not only are bonding opportunities good but the charge of the electrophile becomes distributed over much of the aromatic system, thus further reducing the energy.

One may perform a simple geometric calculation corresponding to the situation in figure 4. From different values assumed for the angle between the carbon-electrophile bond and the axial direction, θ, and a knowledge of the metal-ring distance and ring size, the C-E distance for a symmetrical positioning of the electrophile in the equatorial plane may be calculated. Figure 5 shows the geometrical relationship between the variables. Also, the metal-electrophile distance, M-E, may be obtained. Table IV lists

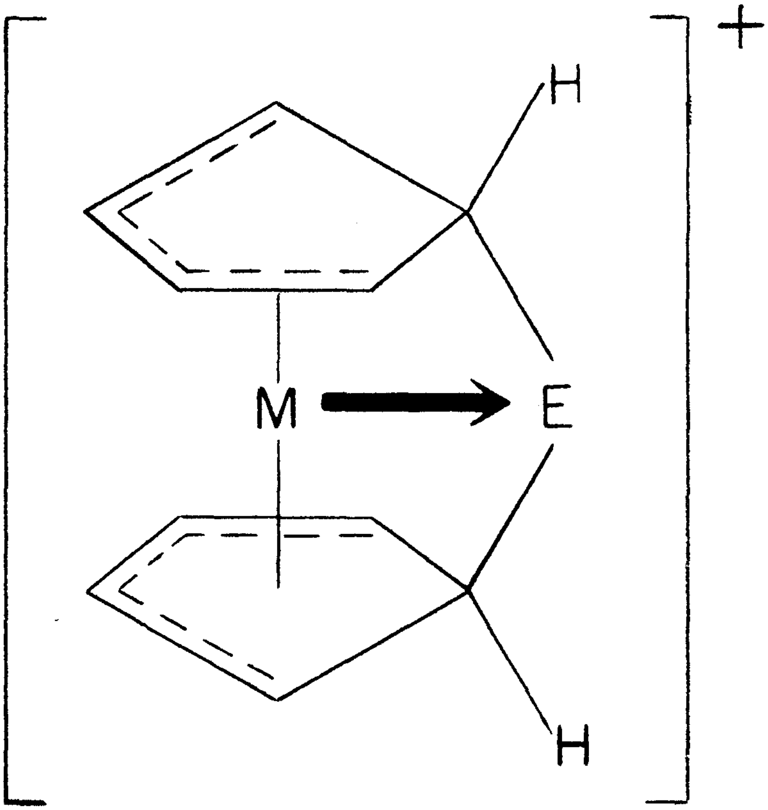
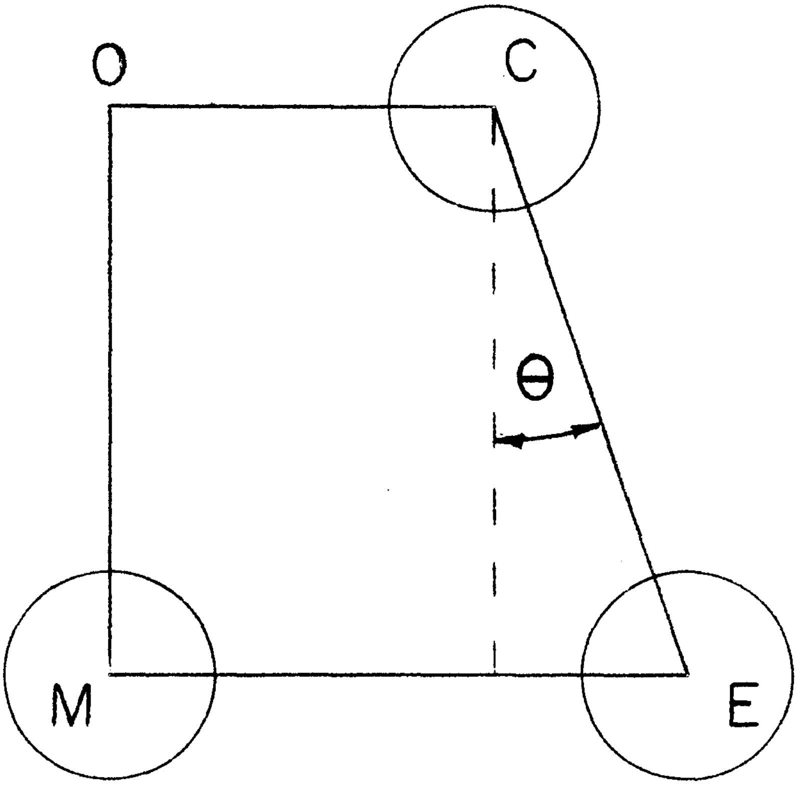


Figure 4.



$$\overline{CE} = \overline{OM}\sec\theta$$

$$\overline{ME} = \overline{OC} + \overline{CE}\sin\theta$$

Figure 5.

TABLE IV

Electrophile Bond Distances

OM,Å	θ°	CE,Å	ME,Å
1.69	0	1.69	1.22
	5	1.70	1.37
	10	1.72	1.52
	15	1.75	1.67
	20	1.80	1.84
	30	1.95	2.20
1.84	0	1.84	1.22
	5	1.85	1.38
	10	1.87	1.54
	15	1.90	1.71
	20	1.96	1.89
	30	2.12	2.28

results of this calculation for ferrocene and ruthenocene, since for these metallocenes the perpendicular distance between the center of the metal and a ring has been determined from x-ray diffraction studies on crystals as 1.69Å for ferrocene (62,63), 1.84Å for ruthenocene (62), and 1.85Å for osmocene (64). The distance from the center of the ring to a ring carbon has been taken equal to 1.22Å (calculated from the known C-C distance for the cyclopentadienyl rings). The value of θ which corresponds to a carbon tetrahedral bond angle is 19°28', and for this angle for the case of ferrocene (OM = 1.69Å) the CE distance is comparable to the ME distance, namely 1.80Å as compared to 1.84Å. The MC distance is 2.05Å from the x-ray crystallographic data (62). It is significant that the ME distance for a tetrahedral angle for ferrocene compares favorably with the Fe-C distance of 1.84Å for iron pentacarbonyl. One concludes that geometrical factors allow good bonding between the ferrocene system and the electrophile since bond angles and bond distances appear favorable.

In ruthenocene and osmocene the situation is less clear. The MC distances are 2.21Å (62) and 2.22Å, respectively. Data on the metal-carbonyl distances in carbonyl derivatives is not available for comparison. However, for any value of θ the CE distance must be considerably longer than in ferrocene which means that carbon-electrophile bonding is weaker for equatorial bonding of the electrophile to the metal. Skewed configurations would allow the bonding of the electrophile to one ring and the metal, but bonding to the opposite ring would be correspondingly reduced.

There have been some results which suggest the possibility of an intermediate with the electrophile bonded to the central metal besides the solvolysis data mentioned in the Introduction. Ferrocene appears to protonate at the metal as evidenced by nuclear magnetic resonance studies (50,66). Also, dicyclopentadienylrhenium hydride is known in which the hydride hydrogen is bonded to the central rhenium atom (67,68). This hydride may be protonated forming a stable ion whose salts are isolable. The additional hydrogen is also attached to the central metal (67,68). The solvolysis of the tosylate of β-hydroxy-1,1'-

trimethyleneferrocene, an ester which has the reactive center favorably situated for metal participation, was notably faster than cyclopentyl tosylate (49).

If one considers now the electrophile structure, it is seen that the acylonium ion has a net electron density deficit at the acyl carbon p-orbital and may, therefore, bond with electron rich centers of the metallocene. The acylonium ion is linear if effects of the aluminum tetrachloride ion, which may be paired with the acylonium ion, are neglected. Only two groups, the carbonyl oxygen and an alkyl or aryl group, are bonded to the electrophilic carbon. On the other hand, a trigonal alkyl carbonium ion has three groups, hydrogens and/or alkyl groups, surrounding it and adding to the effective bulk. Ion pair formation in each case may also increase the effective bulk. It seems reasonable to expect reactions of the alkyl carbonium ion to be more susceptible to steric hindrance than those of the acylonium ion. Alkylation of ferrocene is well known to be more difficult to accomplish than acylation (12,69,70). There are no good data to tell whether t-butylation is more difficult to effect than ethylation of ferrocene. However, Russian workers have performed some yield studies which do not show any substantial differences between n-alkylation and t-alkylation (7).

The dimethylaminomethylene carbonium ion (fig. 6) is also trigonal. However, aminomethylation of ferrocene is

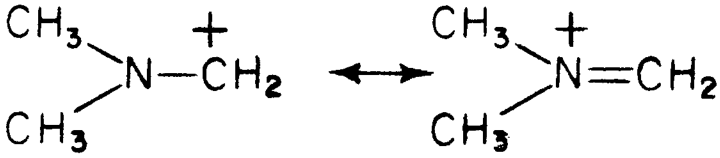


Figure 6.

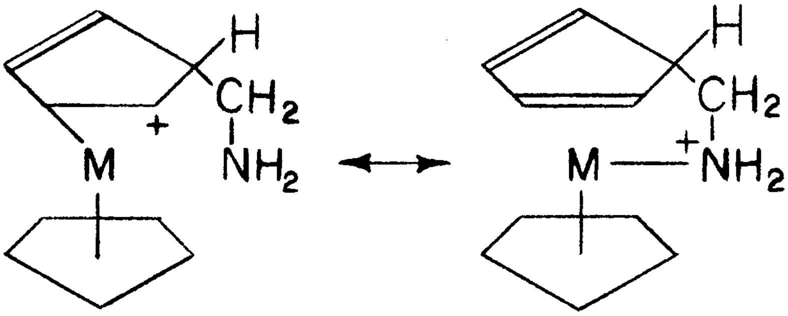
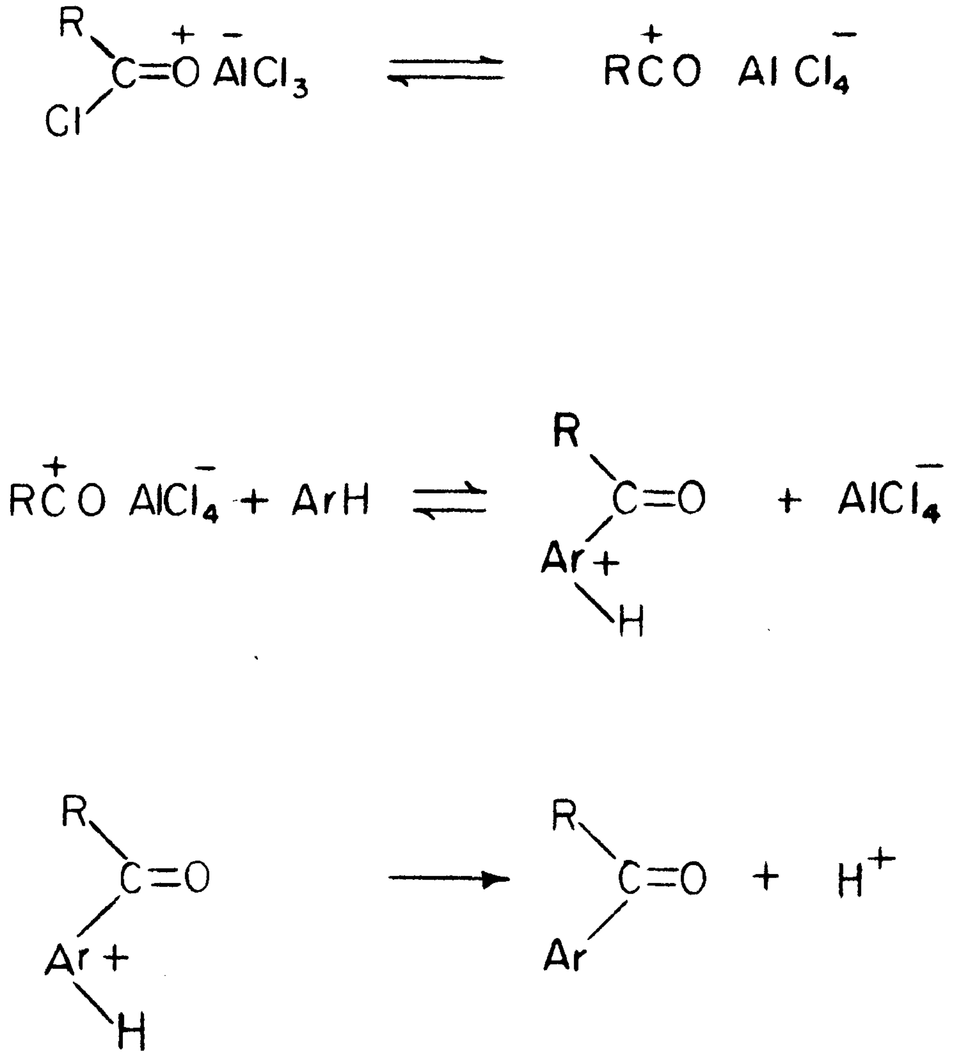


Figure 7.

reasonably facile (38,71). Formylation with N-methylformanilide and phosphorous oxychloride occurs even more readily, and only a few hours at a moderately warm temperature are required for good yields of aldehydes (16,18,33,34,35). These electrophilic reagents may be less sterically crowded due to the absence of ion-pairing. Also, the difference between alkylation and aminomethylation or formylation may be due to the specific role that the nitrogen may play in bonding to the central metal while the electrophilic carbon interacts with the ring carbons (fig. 7).

3.2 Mechanisms of Electrophilic Metallocenyl Substitution

Although the mechanisms of electrophilic substitution of metallocenes have not as yet been worked out, the mechanism of Friedel-Crafts acetylation is probably similar to that for benzene. Certain details of the benzene mechanism of acylation with aluminum trichloride catalyst which concern the nature of the attacking electrophile remain to be cleared up, but the formulation of figure 8 is representative and probably the most likely of the mechanisms (72). Analogous to the benzene mechanism, acetylations of metallocenes catalyzed by boron trifluoride may proceed as in figure 9. Another possible mechanism would replace equation 9 with two steps (fig. 19), and would introduce an intermediate such as is involved in benzene ring substitutions. A further mechanistic possibility should be mentioned,



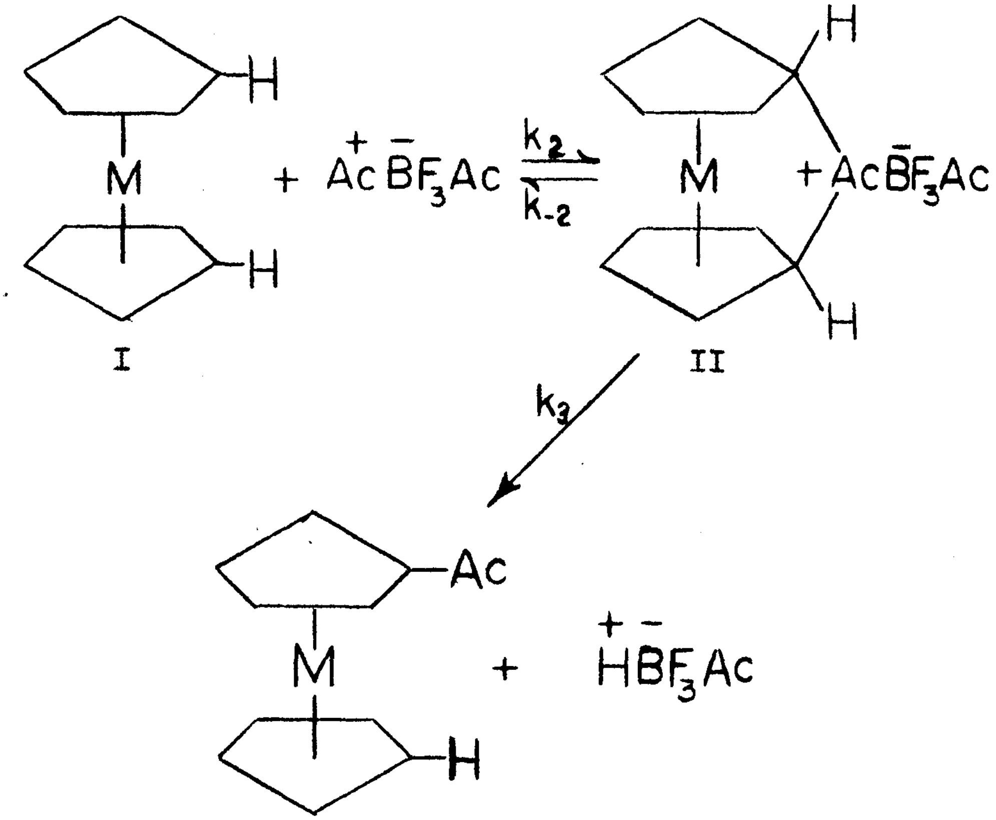
(4)

(5)

(6)

Figure 8.

$$Ac_2O + BF_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{+}{Ac}\overset{-}{B}F_3Ac \qquad (7)$$

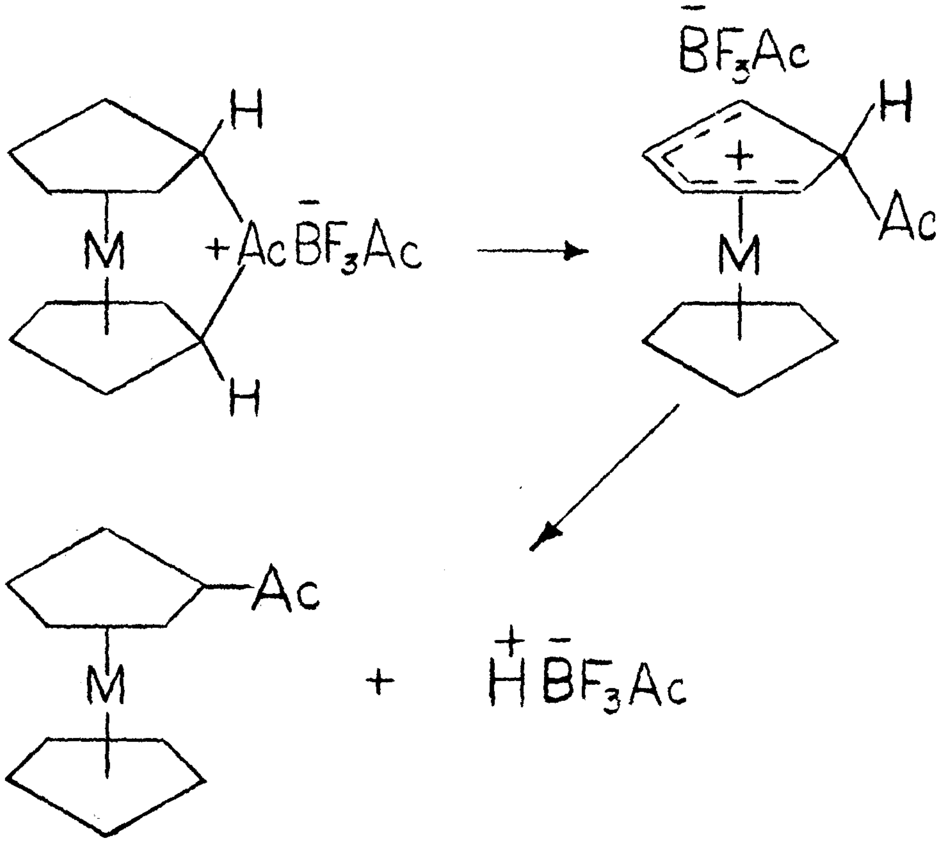


(8)

(9)

$$\overset{+}{H}\overset{-}{B}F_3Ac \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} HOAc + BF_3 \qquad (10)$$

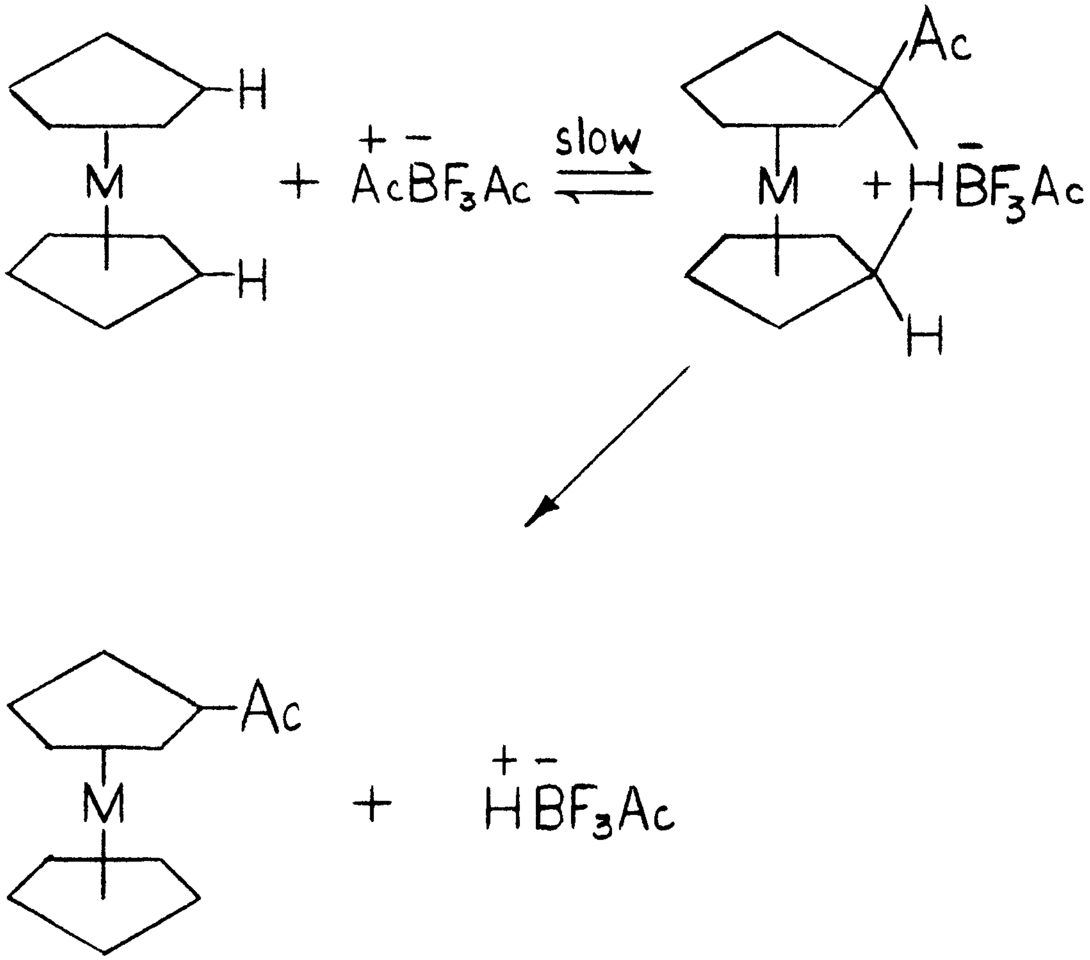
Figure 9.



(11)

(12)

Figure 10.



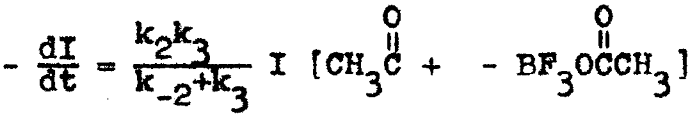
(13)

(14)

Figure 11.

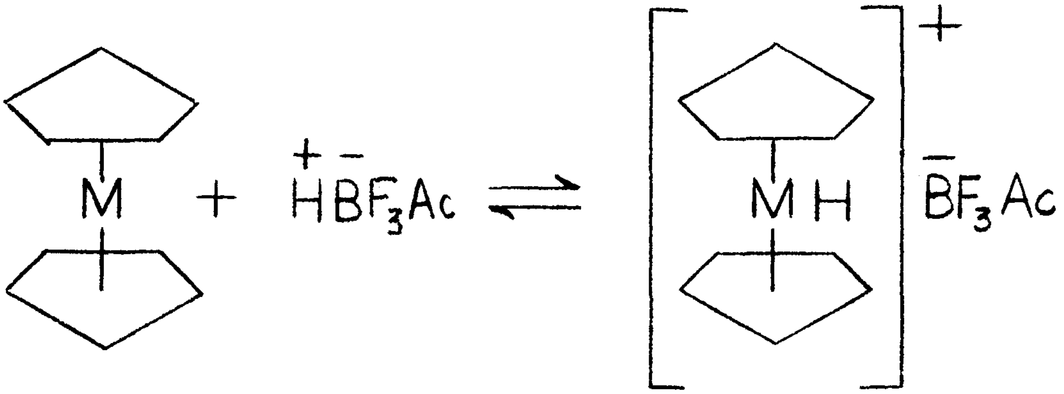
namely that the leaving proton bridges the aromatic system as in figure 11. This latter mechanism involves approach of the electrophile from the top; the transition state would resemble figure 4. If the steps are reversible, any of these mechanisms could account for the retardation of acetylation and diacetylation in the presence of acid (73).

If the steady state assumption is made for the intermediate II (fig. 9), the rate will be given by equation 15.



$$-\frac{dI}{dt} = \frac{k_2k_3}{k_{-2}+k_3}\, I\, [\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}} + \quad - \mathrm{BF_3O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_3}] \tag{15}$$

This result justifies the use of equation 1 for calculating relative rates. It has been suggested that metallocene is removed from the acetylation reaction through formation of a stable, non-acylable complex with the Lewis acid catalyst and a proton source (73) (fig. 12). If such is the case, the method used for obtaining relative rates is considerably compromised since different metallocenes may complex to differing degrees. The results of the present work show that ferrocene is not as strong a base as solvent acetic acid, but that when an acetic acid solution of ferrocene is made quite concentrated in boron trifluoride gas a purple colored complex involving ferrocene is formed. Therefore, the equilibrium of equation 16 (fig. 12) is important at sufficiently high concentrations of boron trifluoride.


M
+
$\overset{+}{H}\overset{-}{B}F_3Ac$
$\rightleftharpoons$
MH
+
$\overset{-}{B}F_3Ac$

(16)

Figure 12.

3.3 Relative Reactivities of Ferrocene and Ruthenocene

Ruthenocene is a weaker base than ferrocene and as a result is not removed from the acetylation reaction by protonation to the degree that ferrocene is (50,66). If protonation of ruthenocene in competitive acetylation with ferrocene does not occur extensively in relation to ferrocene, then one must explain otherwise the fact that ferrocene is an order of magnitude more reactive. The geometric result developed in Section 3.1 provides a basis for discussing this reactivity difference. From Table IV it is seen that the perpendicular distance between the rings increases as the size of the metal increases. As far as bonding to the rings is concerned, this means that the electrophile must bridge a greater expanse in the heavier metallocenes. If a bridged structure is to be maintained (fig. 4), either the structure will become skewed or bonding to the rings will be weakened although bonding to the central metal may be able to partially make up for the loss of bonding energy. The most favorable situation exists for ferrocene where bonding to both rings and metal may occur simultaneously with favorable bond angles being formed.

3.4 Alkyl Substituent Effects

Further evidence for the participation of metal orbitals in electrophilic metallocenyl substitution might come from a study of substituent effects on the reaction.

If ring orbitals are not exclusively involved in the release of electrons to the electrophile, then a reduced magnitude might be expected for a substituent effect. Complicating factors arise, however. If little charge separation is accomplished in the transition state then little electron release from ring substituents is required. Effects of methyl substitution in solvolyses of benzyl derivatives becomes more pronounced as the solvolyses become more limiting, and very large factors may be found (see the discussion in ref. 49). The hydrolyses of ferrocenylcarbinyl acetates is limiting (49). However, the hydrolysis of methyl (3-methylferrocenyl)carbinyl acetate is faster than methylferrocenylcarbinyl acetate by a factor of only three or four (40). It would appear that considerable metal orbital participation is involved.

It was found that 1,1'-diethylferrocene is only slightly more reactive than ferrocene (α-position 1.4 times more rapid, β-position 2.8). Toluene is benzoylated (75) 110 times more rapidly than benzene with aluminum trichloride in benzoyl chloride at 25°. Acetylation with aluminum trichloride at 0° indicates toluene to be 13.3 times more reactive than benzene (76). In ethylene chloride solution at 25° ethylbenzene is benzoylated about 100 times faster than benzene and is acetylated more rapidly than benzene by a factor of 130 (77). The partial rate factor for the <u>para</u>-position in ethylbenzene relative to a single position in benzene is 750! It is apparent that electron release from a ring ethyl in ferrocene during acetylation is small when compared to benzene. This fact may be interpreted to support the metal participation hypothesis.

The acetylation of 1,1'-diethylferrocene gives only twice as much β-substitution as α-substitution. The acetylation of 1,1'-dimethylferrocene also gives twice as much β-substitution whereas 1,1'-diisopropylferrocene gives four to five times more β-substitution (58). Probably the major factor operating in this latter case is steric hindrance at the α-position due to the increased bulk of the isopropyl group. Simple molecular orbital approximations made for substituent effects in metallocenes indicates that the α-position should be more reactive than the β-position in electrophilic substitution (78). However, it has been found that the β-position is more readily substituted (58,79). This is explained by the operation of steric hindrance at the α-position due to the alkyl group.

If the low selectivity of 1,1'-dialkylferrocenes towards acetylation is not due entirely to steric effects, then the product ratio indicates again the high reactivity of metallocenes in accord with Brown's selectivity principle. The β-position in ferrocene may be likened to the <u>para</u>-position in benzene, and the α-position likened to the <u>ortho</u>-position in benzene. The acetylation of ethylbenzene gives a <u>para/ortho</u> product ratio of 323. Since the CCC bond angle in ferrocene is 72° and in benzene is 60°, the steric effect of an ethyl group should be less in ferrocene (58). Thus, since the product ratio for 1,1'-dialkylferrocenes is considerably smaller than for ethylbenzene, the high reactivity of ferrocene is evidenced.

3.5 ω-Ferrocenylalkanoic Acids

The pK_A's* of ferrocene carboxylic acid (24,58), ferrocene-1,1'-dicarboxylic acid (1,24) 1,1'-dimethyl-2-ferrocenylcarboxylic acid (58), and 1,1'-dimethyl-3-ferrocenylcarboxylic acid (58) have been determined previously in solvents such as water, "66%" ethanol, and "66%" dimethylformamide (14,24). Since marked solvent dependency is exhibited by acid strength (81) and because the above workers report no accurate physical properties of the ethanol-water solvents used, comparison of previous results with the acid strengths of ω-ferrocenylalkanoic acids as determined in this work is considerably hampered. However, the data obtained for the ω-ferrocenylalkanoic acids are internally consistent and revealing (see Table I).

Although weaker acids than the corresponding benzene derivatives, the ω-ferrocenylalkanoic acids follow the same order of acid strength as for the benzene series as

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*In reference 58 the pK_A values reported for "66%" ethanol have been obtained through an erroneous conversion from k_A. This may also be the case for the "66%" dimethylformamide data.

is shown by a comparison of values in Table I with Table V for the pK_A's of benzene derivatives in water at 25.0°.

TABLE V

pK_A in Water at 25.0°

Acid	pK_A	Ref.
$C_6H_5CH_2COOH$	4.31	82
$C_6H_5(CH_2)_2COOH$	4.66	83
$C_6H_5(CH_2)_3COOH$	4.76	83

In contrast to the oft quoted result of Woodward, Rosenblum, and Whiting (1) that the first dissociation constant of ferrocenedicarboxylic acid is nearly identical to that for benzoic acid, the difference between the strengths of ferrocenecarboxylic acid and benzoic acid obtained in the present work is quite large. Ferrocenecarboxylic acid has a pK_A of 6.6 whereas the pK_A of benzoic acid is 6.1 (see Table I) corresponding to a difference in energy of 655 cal/mole. A similar difference was also found between ferrocenylacetic acid and phenylacetic. The ferrocene derived acids may be stabilized relative to the phenyl derivatives by metal interaction with the carboxyl group. Electron release to the carboxyl carbon or hydrogen bonding of the hydroxyl to the metal are both possible sources of stabilization. On the other hand, the difference might be taken to mean that the carbocyclic rings of ferrocene are negatively charged which would result in an energy of repulsion in the carboxylate anion. Since the difference in ground state energies of ferrocenecarboxylic acid and benzoic acid cannot be accurately assessed, a calculation of the amounts of charge separation is not possible.

3.6 Solvolysis of ω-Ferrocenyl-1-alkyl Arylsulfonates

The results of the solvolysis of ω-ferrocenyl-1-alkyl arylsulfonates will be examined in the following sections in terms of the possibility of the occurrence of ferrocenyl participation in the solvolysis reaction. Comparisons between ferrocenyl participation and phenyl and substituted phenyl participation will be made. The latter two forms of aryl participation have been well studied by Winstein and coworkers (44, 46, 59, 84) and will be reviewed in the following section prior to a comparison with ferrocenyl systems.

3.6.1 Phenyl Participation

Heck and Winstein (59) have used the following as evidence for aryl participation in solvolysis of arylalkyl arylsulfonates: i) rate enhancement of 4-aryl-1-butyl esters relative to systems in which ring size effects prevent participation, such as 3-aryl-1-propyl and 5-aryl-1-pentyl esters; ii) formation of tetralin derivatives among the products; iii) rate enhancement due to methoxyl substitution on the phenyl groups; iv) reduced entropies of activation relative to solvolyses of n-alkyl esters where participation cannot occur.

3.6.1.1 Rate as a Function of Alkyl Side-Chain in Phenyl Systems

The solvolysis rates of certain ω-aryl-1-alkyl arylsulfonate esters vary with the length of the alkyl chain in a way which may be explained in terms of neighboring group participation (59). Table VI shows the relative rates of some ω-phenyl-1-alkyl arylsulfonates. Except for the formolysis of 2-phenyl-1-ethyl arylsulfonates, no rate increases for the phenyl derivative relative to the n-alkyl arylsulfonates are in evidence. Table VII contains data for a series of ω-(2,4,dimethoxyphenyl)-1-alkyl-p-bromobenzenesulfonates. Here significant rate increases are evident for all chain lengths below five carbons, and an especially large relative rate is found for the formolysis of 2-(2,4-dimethoxyphenyl)-1-ethyl p-bromobenzenesulfonate (84). Similar results, although less pronounced, are observed in the anisyl systems (Table VIII).

The solvolysis rate differences between ω-aryl-1-alkyl systems of varying alkyl chain length may be due to i) a decreasing inductive effect of the aryl group as the side chain length increases and the aryl group is progressively removed from the reaction center, ii) differing solvation energies as the aryl group is removed from the vicinity of the reaction center, and iii) participation of the aryl group in the ionization process. The phenyl group has an electron withdrawing inductive effect relative to hydrogen; and to the extent that the inductive effect is important, the ionization rate will increase as the phenyl group is removed from the ionizing center.

The steric effect of the phenyl group is to hinder solvation of the reaction center. This steric effect dictates that removal of the phenyl group from the reaction site with increasing chain length will increase the solvolysis rate. Both the inductive and steric factors are expected to become unimportant for chain lengths of three or more carbons. At least for certain chain lengths in some solvents, phenyl participation does influence the solvolysis rate. The alkyl chain length is critical since ring size must be proper to allow participation.

2-Phenyl-1-ethyl p-toluenesulfonate solvolyzes at approximately one-third the rate of ethyl p-toluenesulfonate in acetic acid at 75° (Table VI). This rate comparison suggests that the inductive and steric effects of the phenyl

TABLE VI

Relative Rates of Solvolysis of ω-Phenyl-1-alkyl *p*-Toluenesulfonates and *p*-Bromobenzenesulfonates at 75°

p-Toluenesulfonate	AcOH	HCOOH
ethyl	1	1
2-phenyl-1-ethyl	0.37	2.0
p-Bromobenzenesulfonate		
n-butyl	1	1
n-propyl	1.1	-
2-phenyl-1-ethyl	0.57	2.8
3-phenyl-1-propyl	0.72	0.56
4-phenyl-1-butyl	0.98	0.96
5-phenyl-1-pentyl	1.0	0.95

TABLE VII

Relative Rates of Solvolysis of ω-(2,4-Dimethoxyphenyl)-1-alkyl p-Bromobenzenesulfonates at 75° (59)

p-Bromobenzenesulfonate	AcOH	HCOOH
n-butyl	1	1
2-(2,4-dimethoxyphenyl)-1-ethyl	423	1900
3-(2,4-dimethoxyphenyl)-1-propyl	2.7	-
4-(2,4-dimethoxyphenyl)-1-butyl	4.2	9.5
5-(2,4-dimethoxyphenyl)-1-pentyl	1.1	1.0

TABLE VIII

Relative Rates of Acetolysis of ω-(4-methoxyphenyl)-1-alkyl p-Bromobenzenesulfonates at 75° (59)

p-Bromobenzenesulfonate	Rel. Rate
n-butyl	1
2-(4-methoxyphenyl)-1-ethyl*	53
3-(4-methoxyphenyl)-1-propyl	0.77
4-(4-methoxyphenyl)-1-butyl	1.3

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* See references 46, 59, and 85.

group are determining influences on the acetolysis rate. In formic acid, however, the rate sequence is reversed. Here the 2-phenyl-1-ethyl p-toluenesulfonate solvolyzes twice as fast as the unsubstituted ethyl p-toluenesulfonate, a result which suggests that neighboring group participation is important. Other evidence such as the formation of rearranged products and the magnitude of $\Delta S^{\ddagger}$ (both criteria are discussed in the following sections) support the hypothesis of phenyl group participation in the formolysis of 2-phenyl-1-ethyl sulfonate esters.

Both the acetolysis and formolysis of 2-(2,4-dimethoxyphenyl)-1-ethyl p-bromobenzenesulfonate exhibit marked rate increases over the rates of n-butyl and the corresponding 5-aryl-1-pentyl esters. Aryl participation is quite evident in this 2-arylethyl derivative (84).

The relative rates for the acetolysis and formolysis of the other ω-phenyl-1-alkyl sulfonates do not indicate that phenyl participation is occurring. For the 2,4-dimethoxyphenyl series, on the other hand, aryl group participation accounts for the increase in solvolysis rate of 4-(2,4 dimethoxyphenyl)-1-butyl p-bromobenzenesulfonate over the n-butyl and 5-aryl-1-pentyl esters (59). The participation of an ortho methoxyl group in 3-(2,4-dimethoxyphenyl)-1-propyl p-bromobenzenesulfonate accounts for the rate increase observed for this derivative (59).

The rate sequence *n*-alkyl$\leq$arylpentyl$<$arylbutyl$<$arylethyl (for aryl = substituted phenyl) is indicative of aryl group participation in the ethyl and butyl compounds. The above sequence is determined primarily by ring size effects (59, 86, 87). For certain favorable side-chain lengths, aryl participation may occur with a minimum of internal strain and unfavorable steric interactions. The rate effect is generally larger for the 2-aryl-1-ethyl system than for the 4-aryl-1-butyl system.

3.6.1.2 Product Composition in Phenyl Systems

The nature of products produced from solvolysis reactions often provides further support for the occurrence of neighboring group participation. The presence in the product mixture of rearranged products (also of rearranged starting materials) is the supportive evidence generally sought. Evidence of this kind is never sufficient in itself, for if neighboring group participation is defined as a rate enhancement due to the involvement of the neighboring group in the reaction, rearrangement may occur with or without rate enhancement, i.e. after the rate determining step. If, however, rate enhancement and migration of a likely neighboring group are concurrent, neighboring group participation is a likely explanation of the experimental results.

Migration of the phenyl group in the 2-phenyl-1-ethyl system occurs to the extent of 10% in acetolysis and about 45% in formolysis as is evidenced by labeling experiments (88, 89). These results are in agreement with the hypothesis of predominant neighboring phenyl participation in formolysis of 2-phenyl-1-ethyl p-toluenesulfonate (46).

Aryl participation in the 4-aryl-1-butyl system (59, 86) (Ar_1-5 and Ar_2-6 participation) might be expected to lead to tetralin derivatives among the products. Indeed, such is the case as is summarized in Table IX.

The extent to which tetralin formation parallels participation may be examined (59) since it is likely that solvolysis proceeding with Ar_1-5 participation always produces tetralin. The tetralin obtained from the solvolysis of 4-phenyl-1-butyl p-bromobenzenesulfonate was assumed to be formed from that part of the solvolysis which proceeds by way of aryl participation, and the anchimerically unassisted solvolysis (solvent participation) was assumed not to produce tetralin (59). With these assumptions and a knowledge of the overall rate constant and the product distribution, it was possible to dissect the overall rate constant into the rate constant for anchimerically assisted solvolysis and the rate constant for anchimerically unassisted solvolysis. If the foregoing assumption that tetralin products are produced exclusively by aryl partici-

TABLE IX

Tetralins from Formolysis at 75° (59, 86)

p-Bromobenzenesulfonate	% Tetralin in Product
4-phenyl-1-butyl	19
4-(4-methoxyphenyl)-1-butyl	54
4-(2,4-dimethoxyphenyl)-1-butyl	91
4-(3,5-dimethoxyphenyl)-1-butyl	88

pation is made, and the additional assumption that methoxyl substitution affects only assisted sovolysis is made, then use of the rate constant for anchimerically unassisted solvolysis (obtained as described above for 4-phenyl-1-butyl p-bromobenzenesulfonate) enabled the authors to calculate the amounts of tetralin products formed in the solvolyses of 4-(4-methoxyphenyl)-1-butyl and 4-(2,4-dimethoxyphenyl)-1-butyl p-bromobenzenesulfonates (59). The calculated and observed product distribution were in very good agreement (within experimental error). In the phenyl systems, then, if one allows the assumptions made, Ar_1-5 participation leads exclusively to tetralin products.

3.6.1.3 Effect of Methoxyl Substitution on Rate and Product

Methoxyl substitution of the benzene ring of the 2-phenyl-1-ethyl system and the 4-phenyl-1-butyl system leads to increases in the anchimerically assisted sovolysis rates although the effect is less pronounced in the latter system (59). Rate increases due to methoxyl substitution are probably due to the activating effect of a methoxyl group upon the benzene aromatic system. Other activating substituents or active aromatic systems are expected to show similar enhancements of anchimerically assisted rates.

3.6.1.4 Entropy of Activation as an Indication of Participation

The entropy of activation of a solvolysis reaction may be used as a criterion for participation (59, 84). For an unassisted solvolysis (solvent participation alone) $\Delta S^{\ddagger}$ is generally 18 ± 2 entropy units, whereas for an assisted solvolysis $\Delta S^{\ddagger}$ tends to be lowered to 7 ± 2 entropy units. Thus, $\Delta S^{\ddagger}$ for the acetolysis of 2-phenyl-1-ethyl p-toluenesulfonate and for ethyl p-toluenesulfonate is about 17 entropy units. In formic acid $\Delta S^{\ddagger}$ for the ethyl ester does not change appreciably, but $\Delta S^{\ddagger}$ for the 2-phenyl-1-ethyl ester is reduced to 9.5 entropy units. The effect is not as great in the 4-aryl-1-butyl system. Acetolysis of 4-phenyl-1-butyl p-bromobenzenesulfonate has $\Delta S^{\ddagger}$ of 16.8 entropy units, the anisyl derivative only drops to 15 entropy units, and the 2,4-dimethoxyphenyl derivative to 10.7 entropy units (59).

3.6.1.5 Effect of Solvent

It is apparent from what has gone before that aryl participation is strongly solvent dependent. Formolysis results in relatively more participation than does acetolysis (59). This is reflected in all of the criteria discussed in the preceding sections.

The results of Bartlett and Bank (90) illustrate the importance of the choice of solvent. Both 2-cyclopentyl-1-ethyl and 2-(Δ^3-cyclopentenyl)-1-ethyl p-toluenesulfonates were solvolyzed in solvents of similar ionizing power but differing nucleophilicities. The ratio of the rate of 2-(Δ^3-cyclopentenyl)-1-ethyl p-toluenesulfonate to that of 2-cyclopentyl-1-ethyl p-toluenesulfonate was taken as an approximate measure of rate enhancement due to participation of the double bond. This ratio increased by a factor of more than 300 upon going from the most nucleophilic solvent (50% ethanol) to the least nucleophilic solvent (98% formic acid). This change was primarily due to a decrease in solvent participation as the nucleophilicity of the solvent was decreased.

3.6.1.6 Nature of the Transition State for Phenyl Participation

All of the present evidence supports the hypothesis of unsymmetrical bridging by the participating aryl group. When ring size and electronic factors permit participation, the bond between the aryl group and the ionizing center is only partially formed in the transition state and is stretched relative to the normal C-C bond distance.

For the 2-aryl-1-ethyl system, the evidence for weak aryl group bonding consists of the fact that no β-deuterium isotope effect is observed for the solvolysis of 2-phenyl-

1-ethyl, 2-(p-methoxyphenyl)-1-ethyl, and 2,2-diphenyl-1-ethyl p-toluenesulfonates (88, 91); this indicates that bond changes do not become communicated to the β-carbon-hydrogen bonds in the transition state. Furthermore, the rate differences observed between the diastereomers of the 3-phenyl-2-butyl system and related systems are small (92). Larger rate differences would be expected if a symmetrically bridged ion is formed in the transition state since the differences in non bonding repulsions of the diastereomers would be large (methyl eclipsing a methyl versus a methyl eclipsing a hydrogen).

For the 4-aryl-1-butyl system the rate effects of methoxyl substitution are small, which suggests that the involvement of the aryl group is small (59). Corey and Sauers (87) in a consideration of ring size effects also conclude that only weak bonding exists between the carbonium ion center and the aryl group.

3.6.2 Ferrocenyl Participation

In the present work, the criteria used in the search for ferrocenyl participation were: i) comparison of the rates of solvolysis in the ω-ferrocenyl-1-alkyl series; ii) comparison of solvolysis rates of ferrocenyl with phenyl systems; iii) examination of products of solvolysis. No ferrocenyl participation was found in the 3-ferrocenyl-1-propyl, 4-ferrocenyl-1-butyl, and 5-ferrocenyl-1-pentyl systems in acetolysis and hydrolysis. The entropies of activations were not obtained, since a side reaction due to oxidation is rampant at temperatures above 100°. Below these temperatures, rates are inconveniently slow, and oxidation becomes serious because of the extended times required.

The solvent system, 80% acetone-water, although not conducive to aryl participation, was studied briefly since oxidation was absent.

3.6.2.1. Rates of Solvolysis

An examination of Table II (page 14) and Table III (page 16) reveals that the rates of acetolysis and hydrolysis of the ω-ferrocenylalkyl p-bromobenzenesulfonates studied do not differ significantly from the corresponding phenyl derivatives. Furthermore, only minor rate differences exist between the 3-ferrocenyl-1-propyl, 4-ferrocenyl-1-butyl, and 5-ferrocenyl-1-pentyl sulfonates. The fact that the propyl derivative solvolyzes a little slower than the other two alkyl derivatives studied may be attributed to the inductive and bulk effects of the ferrocenyl group when removed from the reaction center by only two carbons. No rate enhancement is found for the ω-ferrocenyl-1-alkyl derivatives studied. It is possible that ferrocenyl participation would become evident in a solvent system other than the acetic acid or aqueous acetone used in this work. It is significant, however, that in acetic acid no rate enhancement for ω-ferrocenyl-1-alkyl derivatives is found whereas the solvolysis rate of 4-anisyl-1-butyl p-bromobenzenesulfonate in this solvent is measurably enhanced.

Aryl participation may be thought of as being an electrophilic alkylation of an aromatic system, i.e. an electrophilic aromatic substitution. Ferrocene has been shown to be an extremely reactive aromatic system towards certain electrophilic substitutions. In acetylation, for example, ferrocene is at least ten times more reactive than anisole (18). The high reactivity of ferrocene towards electrophilic substitution suggests that the ferrocene nucleus could function as an especially effective neighboring group if other factors such as ring size and steric hindrance would permit. The absence of rate enhancement in the ω-ferrocenyl-1-alkyl sulfonates studied strongly suggests the absence of participation of the type that occurs in phenyl derived systems. Apparently the appropriate rings for participation cannot be formed in the ω-ferrocenyl-1-alkyl derivatives (with the possible exception of the 2-ferrocenyl-1-ethyl system as discussed below).

Trifan has studied the solvolysis of 2-ferrocenyl-1-ethyl p-toluenesulfonate (45). The rate is greater for 2-ferrocenyl-1-ethyl p-toluenesulfonate than for the corresponding phenyl derivative by a factor greater than 500.

A comparison of this rate with that for the hydrolysis of 4-ferrocenyl-1-butyl *p*-bromobenzenesulfonate (Table III, page 16) is possible since the solvent systems (80% acetone-water) are probably the same. In the 4-aryl-1-butyl systems, there are no significant rate differences between ferrocenyl and phenyl derivatives.

Thus, it appears that the ferrocenyl group is able to provide anchimeric assistance in the 2-ferrocenyl-1-ethyl system studied by Trifan but not in the other ω-ferrocenyl-1-alkyl systems. In the former case, the bond angle strains and non-bonding interactions within the ring formed as the ferrocenyl group participates must not be sufficiently severe to prevent the participation.

The absence of rate enhancement does not preclude possible participation of the ferrocenyl group in the reaction at a step subsequent to the rate determining ionization step. Although such participation would not be evidenced by rates, the products formed may differ from a reaction involving only solvent participation.

3.6.2.2 Products

The products of acetolysis of 4-ferrocenyl-1-butyl *p*-bromobenzenesulfonate were found to contain no detectable 1,1'-tetramethyleneferrocene and 1,2-tetramethyleneferrocene; therefore, at most only a few per cent could have been present. These products would be expected from the loss of a proton from, and collapse of, an intermediate involving the participation of a ferrocenyl ring carbon. The result further supports the hypothesis that participation of the phenyl type (involving a ferrocenyl ring carbon in unsymmetrical bridging) is absent. If participation of one of the ring carbons were to resemble phenyl participation, then hydrocarbon products would be expected (see section 3.6.1.2). The product study does not exclude the possibility that ferrocenyl participation involves: i) the metal followed by subsequent solvent attack and opening to form an acetate; ii) a ferrocenyl ring carbon followed by solvent attack.

3.6.3 Probable Nature of Ferrocenyl Participation

It is seen from the foregoing discussion that metallocenyl participation differs from phenyl participation; for despite the fact that ferrocene is a highly reactive aromatic system, no rate enhancement is observed for any but the 2-ferrocenyl-1-ethyl system (45). A permissible explanation which accounts for this result can be derived from the hypothesis that the reactivity of metallocenes towards electrophilic substitution is due to bonding of the electrophile to the metal (see pages 7 and 24). For bulky electrophiles, F strain (93) between the side of the metallocenyl system and the electrophile becomes important. Figure 13 shows this interaction for alkylation.

An additional factor is important for metallocenyl participation, namely ring-size effects which are due to internal strain for various ring sizes and to different entropies of formation for the rings. The closure of a large ring is less probable than for a smaller ring. Figure 14 shows the situation for metallocenyl participation. The rings which would result from metallocenyl participation for alkyl side-chain lengths of three carbons and greater require more free energy for their formation than is compensated for by the increase in delocalization energy due to the neighboring group participation. Thus, only in the case of 2-ferrocenyl-1-ethyl p-toluenesulfonate where such steric factors do not prohibit ring formation is a rate enhancement during solvolysis observed.

Although the above explanation is not uniquely demanded by the results, it is in accord with the results of this work and the precedent of other work on metal involvement in the reactions of metallocenes.

4. EXPERIMENTAL

All melting points are reported uncorrected. Unless otherwise stated all infrared spectra were taken in carbon tetrachloride.

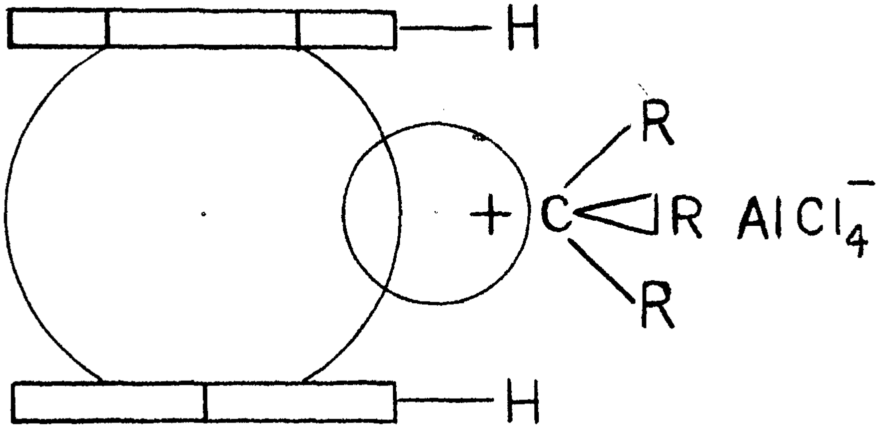

Figure 13.

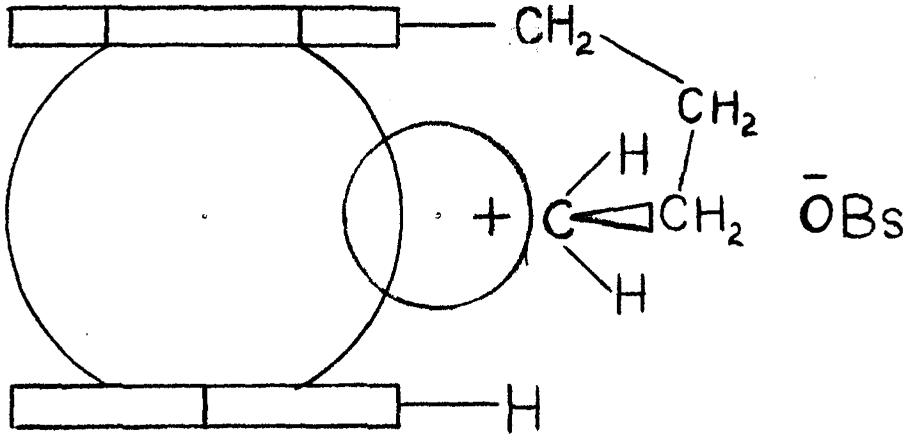

Figure 14.

Ruthenocene (28, 94).--To magnesium metal (6.08 g., 0.25 g. atom) and 100 ml. of anhydrous reagent grade ether stirred under nitrogen in a dry 2 liter flask fitted with an oil sealed stirrer, dropping funnel with nitrogen inlet and efficient condenser bearing a drying tube was added slowly a solution of dried freshly distilled ethyl bromide (20 ml., 0.27 mole) in 70 ml. of anhydrous ether. To this stirred mixture was added over ten minutes a solution of freshly cracked and distilled monocyclopentadiene (21 ml., 0.25 mole) in 75 ml. of dry reagent grade benzene. The solvent was distilled until a reflux temperature of 70° was reached. To the reaction mixture maintained at reflux was added during one hour a solution of ruthenium III acetylacetonate (10.0 g., 0.025 mole) in 150 ml. of dry benzene. The reaction mixture was stirred at reflux for three hours, allowed to stand overnight, hydrolyzed by the cautious dropwise addition of 50 ml. of a saturated solution of ammonium chloride, and then steam distilled. The organic products were extracted from the distillate with ether. The ethereal solution was washed once with water and dried over anhydrous magnesium sulfate. The filtered solution was evaporated and the residue was sublimed under high vacuum at 120°. The sublimate was recrystallized twice from carbon tetrachloride. The mother liquors were chromatographed on 250 g. of alumina and the crystalline solids obtained on evaporation of the benzene eluent were recrystallized from carbon tetrachloride giving a second crop of pure ruthenocene, m.p. 197.5-199°, 19% yield based on ruthenium III acetylacetonate.

Anal. Calcd. for $C_{10}H_{10}Ru$: C, 51.79; H, 4.35. Found: C, 51.77; H, 4.46.

Acetylruthenocene by the BF_3 Method (15, 18, 28, 29).--- Ruthenocene (1.0 g., 0.0043 mole) was dissolved with mechanical stirring in 80 ml. of methylene chloride, the resulting solution cooled in an ice bath to below 5°, acetic anhydride (0.5 ml., 0.0053 mole) added, and the solution saturated with boron trifluoride gas for five minutes during which time the temperature of the solution rose to 15°. The resulting brown solution was stirred in the ice bath for one hour and at room temperature for three hours, cooled in an ice bath and then hydrolyzed by the addition of 200 ml. of saturated sodium acetate solution. The layers were separated, and the aqueous layer was extracted twice with 100 ml. portions of methylene chloride. All methylene chloride solutions were combined, washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solution was filtered, the solvent distilled on the steam bath, and the residue chromatographed on 35 g. of acid-washed alumina with benzene as eluent. Evaporation of the benzene yielded yellow needles which were recrystallized once from n-heptane to give long, fine, yellow needles, 0.55 g., m.p. 115.5-117°. A second crop of needles (0.07 g., m.p. 112-114°) was obtained from the mother liquor giving a total yield of acetylruthenocene of 52%. The infrared spectrum showed a carbonyl absorption at 1680 cm^{-1}. The ultraviolet spectrum in cyclohexane solution showed two absorption maxima at 217 $m\mu$ and 243 $m\mu$ with extinction coefficients of 11,900 and 8,500, respectively; in methanol solution the maxima were shifted to 218 $m\mu$ and 250 $m\mu$.

Anal. Calcd. for $C_{12}H_{12}ORu$: C, 52.61; H, 4.41. Found: C, 52.62; H, 4.50.

Acetylruthenocene by the Phosphoric Acid Method (16, 19, 20)--To a steam bath heated suspension of ruthenocene (1.0 g., 0.0043 mole) in 5.0 ml. of acetic anhydride was added 0.5 ml. of 85% phosphoric acid to give a brown solution which was heated for 10 minutes with occasional shaking. The mixture was cooled to room temperature, poured onto ice, neutralized with sodium carbonate, and allowed to stand for one hour to insure complete hydrolysis of the acetic anhydride. Then the mixture was extracted with methylene chloride until the extracts were nearly colorless. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and the solvent removed from the filtrate by distillation on a steam bath. The residue was chromatographed on 25 g. of acid-washed alumina. Development and elution with benzene afforded a single sharp band. Evaporation of the benzene and a single recrystallization of the crystalline residue from *n*-heptane gave long, thin, cylindrical crystals, 0.95 g. (80%), m.p. 114.5-116° (uncor.).

Competitive Acetylation of Ferrocene and Ruthenocene.-- Ferrocene (0.95 g., 0.0050 mole) and ruthenocene (1.16 g., 0.0050 mole) were dissolved in 75 ml. of methylene chloride (Matheson reagent) and cooled in an ice bath to a temperature below 5°. Acetic anhydride (0.51 ml., 0.0054 mole) was added and the solution was saturated with boron trifluoride for 5 minutes to give a purple color. The cooled mixture was stirred for four hours and then hydrolyzed by pouring into 150 ml. of saturated sodium acetate solution. The layers were separated and the aqueous layer extracted three times with methylene chloride. The combined methylene chloride solutions were washed twice with saturated sodium bicarbonate solution. These washings were yellow colored, and extraction with methylene chloride did not remove the color. The methylene chloride solution was dried over anhydrous magnesium sulfate, filtered, the filtrate evaporated to dryness, and the residue chromatographed on about

20 g. of acid-washed alumina. Two bands were obtained on development with benzene: a leading yellow band and a more diffuse orange trailing band. The yellow band was eluted with the first 100 ml. of benzene; this solution was evaporated to dryness and the solid recrystallized once from *n*-heptane to give yellow platelets, 0.651 g., m.p. 198-199°. The mother liquor contained a yellow crystalline material, 0.319 g., m.p. 189-193°, and which when rechromatographed on alumina with hexane eluent gave only one yellow band, m.p. 198-199°, mixed m.p. with ferrocene 159-164°, total yield of ruthenocene, 84%. The orange band was eluted with 200 ml. of 10% ether - 90% benzene. Evaporation of the solvent gave orange needles, 0.917 g., 80.5% yield, m.p. 81-84°. Recrystallization from *n*-heptane gave clusters of orange needles, m.p. 84-85°. The mother liquor was evaporated to dryness, and the ultraviolet spectrum of the residue in cyclohexane had maxima at 221 mμ and 267 mμ. A barely visible orange band, probably a trace quantity of diacetylferrocene, remained on the column.

1,1'-Diethylferrocene (95).--Lithium aluminum hydride (3.8 g., 0.10 mole) was stirred with 100 ml. of anhydrous reagent grade ether, a solution of anhydrous, powdered aluminum trichloride (13.3 g., 0.10 mole) in 100 ml. of ether was added with stirring, followed by the dropwise addition during one hour of 1,1'-diacetylferrocene (10.0 g., 0.037 mole) dissolved in 250 ml. of dry tetrahydrofuran so that gentle reflux was maintained. The mixture was stirred for an additional 1.5 hours, and then hydrolyzed by the cautious addition of 10 ml. of water followed by 200 ml. of 20% hydrochloric acid. The layers were separated, the organic layer washed with water and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and the ether distilled. The residue was dissolved in 50 ml. of n-heptane and chromatographed on 100 g. of acid-washed alumina. Development with n-heptane produced a single large band and a very small trace of a slower moving band. Distillation of the heptane eluent left a liquid residue (8.0 g., 89% yield) n_D^{20} 1.5788 identified as 1,1'-diethylferrocene by its infrared spectrum.

Competitive Acetylation of Ferrocene and 1,1'-Diethylferrocene.--Freshly chromatographed 1,1'-diethylferrocene (1.209 g., 0.00499 mole) and recrystallized ferrocene (0.930 g., 0.0050 mole) were dissolved in 75 ml. of methylene chloride (distilled from calcium hydride) and acetic anhydride (Baker reagent) (0.526 g., 0.00515 mole). The solution was cooled in an ice bath to below 15° and was then saturated with boron trifluoride for four minutes, during which time the temperature remained below 15° and a purple color was formed. The reaction mixture was stirred in the ice bath for four hours at a temperature of 2-5°, then the cold mixture was poured with stirring into 150 ml. of saturated sodium acetate solution. The aqueous layer was extracted with four 50 ml. portions of methylene chloride, the methylene chloride solutions combined and washed with water, then with saturated sodium bicarbonate solution, and finally with water. The solution was dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in n-hexane and chromatographed on 120 g. of acid-washed alumina to give three bands. The first band was eluted with 150 ml. of n-hexane and gave a yellow-orange solid on evaporation of the solvent, 0.821 g. The second band was eluted with 2% acetone - 98% n-hexane. Evaporation of the solvent gave an orange liquid, 0.778 g., 56% yield. The third band followed the second immediately, and distillation of the solvent left orange needles (0.434 g., 38% yield) whose infrared spectrum was identical with that of acetylferrocene. The second band was rechromatographed on 150 g. of acid-washed alumina packed in benzene; development with benzene produced two bands. The first band was eluted with 500 ml. of benzene. Distillation of the solvent left an orange liquid (0.227 g.) having ultraviolet maxima at 227 mμ and 270 mμ (2-acetyl-1,1'-diethylferrocene). The second band eluted with an additional 500 ml. of benzene gave a dark orange liquid (0.442 g.) with ultraviolet maxima at 233 mμ and 276 mμ (3-acetyl-1,1'-diethylferrocene).

Attempted Titration of Ferrocene in Acetic Acid Solvent.--It was not possible to obtain a titration curve for ferrocene in acetic acid containing 1% of acetic anhydride when titrated with toluenesulfonic acid in anhydrous acetic acid.

Ferrocene Carboxylic Acid (24, 58).--Ferrocenecarboxylic acid was prepared and recrystallized from an isopropyl ether-heptane solvent giving orange-brown needles, softened 210°, decomp. 225°.

Ferrocenylacetic Acid.--Ferrocenylacetic acid was prepared by the Willgerodt procedure (16, 96) m.p. 153-158°.

3-Ferrocenylpropionic Acid.--3-Ferrocenylpropionic acid was prepared by the method of Pauson and Osgerby (38) and recrystallized from di-isopropyl ether, m.p. 117-118°.

Anal. Calcd. for $C_{13}H_{14}O_2Fe$: C, 60.49; H, 5.46; Fe, 21.64. Found: C, 60.16; H, 5.71; Fe, 21.34.

3-Ferrocenoylpropionic Acid.--3-Ferrocenoylpropionic acid was prepared by the method of Rinehart, et al. (96) and was purified by sublimation at 125-150° under vacuum to give large, dark orange prisms, m.p. 172.5-175° with decomp.

4-Ferrocenylbutyric Acid (96).---3-Ferrocenoylpropionic acid (2.0 g., 0.007 mole) was refluxed with 40 g. of Raney Nickel catalyst in 250 ml. of 95% ethanol for two hours. The cooled solution was filtered and ethanol distilled. The residue was taken up in 250 ml. of glacial acetic acid and hydrogenated over 1.4 g. of platinum dioxide catalyst at four atmospheres of hydrogen for six days. The filtered solution was distilled under reduced pressure to give a solid residue which was extracted repeatedly with tetrahydrofuran and ether. The combined extracts were extracted with saturated sodium bicarbonate solution. The basic aqueous extracts were filtered, and the filtrate was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried, filtered, and the filtrate evaporated to near dryness to give orange crystals, m.p. 115-125° (reported for ferrocenylbutyric acid, 115-116°). The infrared spectrum had a single strong carbonyl absorption at 1710 cm^{-1}. Further purification gave a light yellow crystalline solid, m.p. 119-120°.

pK$_A$ Measurements

a. Ethanol-Water Solvent.--Reagent grade 95% ethanol was distilled through a 90 cm. fractionating column packed with "Helipak," b.p. 77.6°/742 mm. Hg. The distilled alcohol was diluted with one-half volume of boiled Puritas distilled water to give an ethanol-water solvent of density 0.8915 ± 0.001 at 25.0° corresponding to 58 wt. % ethanol. The solvent was stored in a bottle protected from atmospheric carbon dioxide.

b. *Sodium Hydroxide.*--Sodium hydroxide pellets (0.4 g.) were dissolved in 1 l. of the ethanol-water solvent to give an approximately 0.1N solution.

c. *Titrations.*--A weighed quantity of carboxylic acid was dissolved in approximately 50 ml. of ethanol-water solvent by stirring. Dry carbon dioxide free nitrogen was bubbled through the solution throughout a titration. The pH was followed with a Leeds and Northrop pH meter and standard glass and calomel electrodes. The pK_A for a given acid was identified with the pH at the end point of a titration. Table I lists the results for the various acids studied.

ω-Ferrocenyl-1-alkyl p-Bromobenzenesulfonates.

3-Ferrocenylpropanol-1 (35).--To 10.0 g. (0.039 mole) of 3-ferrocenylpropionic acid dissolved by stirring in 65 ml. of dry tetrahydrofuran was added dropwise a suspension of 2.0 g. (0.5 mole) of lithium aluminum hydride in 60 ml. of anhydrous ether. The reaction mixture was stirred at room temperature for four hours, then cooled in an ice bath and 15 ml. of ethyl acetate was cautiously added. The mixture was poured into water and acidified with dilute hydrochloric acid. The layers were separated, the aqueous layer extracted with ether, the ether solutions combined, washed with water until neutral, and dried over barium oxide. The mixture was filtered, the ether distilled, the residue dissolved in 25 ml. of methylene chloride and chromatographed on 300 g. of acid-washed alumina packed in pentane. Development and elution was accomplished with ether-pentane mixtures. A single band developed and was eluted with 60%, 70%, and 80% ether-pentane. The solvent was distilled leaving an orange oil, 7.55 g., 80% yield. The infrared had a hydroxyl band at 3630 cm^{-1}. Another preparation yielded 84% of the alcohol. The *p*-toluenesulfonate was prepared by reaction with *p*-toluenesulfonyl chloride in pyridine at 0°. Chromatography on alumina and recrystallization from ethyl acetate-hexane gave orange crystals, m.p. 65-66°.

Anal. Calcd. for $C_{20}H_{22}O_3FeS$: C, 60.31; H, 5.55; Fe, 14.02. Found: C, 60.50; H, 5.68; Fe, 13.98

3-Ferrocenyl-1-propyl p-Bromobenzenesulfonate.--To 5.25 g. (0.0215 mole) of 3-ferrocenylpropanol-1 dissolved in 60 ml. of dry pyridine and cooled to below -5° in an ice-salt bath was added 6.29 g. (0.025 mole) of *p*-bromobenzenesulfonyl chloride. The mixture was stirred in the ice-salt bath for one hour, an additional 2.0 g. (0.008 mole) of sulfonyl chloride was added, and stirring was continued for three hours more at the end of which time the reaction mixture was poured into 300 ml. of ice cold 2N sulfuric acid. The orange-yellow crystalline solid which separated was collected on a filter and washed thoroughly with water. The yield of crude, air-dried material was 8.55 g. (85%), m.p. 99-100° from cyclohexane.

Anal. Calcd. for $C_{19}H_{19}O_3BrFeS$: C, 49.27; H, 4.13; Fe, 12.06. Found: C, 49.36; H, 4.20; Fe, 11.92.

Methyl 3-Ferrocenoylpropionate.--To 54.0 g. (0.29 mole) of ferrocene dissolved in 400 ml. of methylene chloride under an atmosphere of nitrogen was added 40.0 g. (0.30 mole) of anhydrous aluminum trichloride. Stirring was started, and a solution of 26.4 g. (0.20 mole) of -carbomethoxypropionyl chloride (97) in 100 ml. of methylene chloride was added dropwise over a 45 minute period and stirring was continued for an additional hour. The reaction mixture was poured with stirring onto an equal volume of ice and water, the layers were separated, the aqueous layer extracted twice with 250 ml. of methylene chloride, the combined methylene chloride layers washed with three large portions of water and dried over anhydrous sodium carbonate. The mixture was filtered, the filtrate concentrated to 150 ml. and chromatographed on 1200 g. of acid-washed alumina packed in ligroin (b.p. 30-60°). Elution with 5 to 10% acetone-ligroin removed a small amount of ferrocene, and the major dark orange band was eluted with 25 to 35% acetone-ligroin. Distillation of the solvent left a dark orange oil weighing 55.88 g. (90% yield based on acid chloride). On standing several days the oil crystallized to form large dark orange plates and prisms, m.p. 39-42°. The infrared spectrum had bands at 1683 and 1744 cm^{-1}.

Methyl 4-Ferrocenylbutyrate.--To 225 g. of 10 mesh granular zinc was added 300 ml. of water, 15 ml. of conc. hydrochloric acid, and 20 g. of mercuric chloride. The mixture was stirred for five minutes and the aqueous layer was decanted. The amalgamated zinc was washed with 300 ml. of distilled water, and a solution of 38.0 g. (0.127 mole) of methyl 3-ferrocenoylpropionate in 350 ml. of methanol was added followed by 300 ml. of conc. hydrochloric acid. The mixture was stirred and maintained at reflux for 22 hours after which time the infrared spectrum of an aliquot indicated that the reduction was complete. The cooled reaction mixture was poured into 1 l. of water and extracted with several 300 ml. portions of ether until the ether extracts were nearly colorless. The combined ether extracts were washed three times with an equal volume of water, dried over anhydrous magnesium sulfate and filtered. The ether was distilled leaving an orange liquid, 33.24 g., yield

91.8%. The infrared spectrum had a single carbonyl absorption at 1748 cm^{-1} and no hydroxyl band.

4-Ferrocenylbutanol-1.--Methyl 4-ferrocenylbutyrate (33.2 g., 0.116 mole) dissolved in 100 ml. of anhydrous ether was added dropwise to a stirred slurry of 3.5 g. (0.124 mole) of lithium aluminum hydride in 150 ml. of anhydrous ether over a period of ninety minutes. The mixture was stirred an additional hour and then was hydrolyzed by the cautious, dropwise addition of 10 ml. of water followed by 200 ml. of 20% hydrochloric acid. The layers were separated, the aqueous layer extracted with ether, and the combined ether solutions washed with water until the washings tested neutral with Hydrion paper. The ether solution was dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* leaving a liquid residue (29.22 g., 98%) which was dissolved in 100 ml. of methylene chloride and chromatographed on 1000 g. of acid washed alumina packed in ligroin (b.p. 30-60°), to give a single major band which was eluted with 75% ether-ligroin. Distillation of the solvent gave an orange oil which eventually crystallized, 22.3 g., m.p. 47-48.5° with previous softening at 45°. Recrystallization from 75% heptane-ether gave material with a constant melting point, m.p. 49-50°. The infrared spectrum had a hydroxyl band at 3660 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}OFe$: C, 65.14; H, 7.03; Fe, 21.64. Found: C, 66.64; H, 9.65; Fe, 23.24.

The acetate was prepared in the usual manner, and chromatography of the product on alumina gave a single light yellow band, 83% yield. The infrared spectrum showed a carbonyl band at 1747 cm^{-1}. The p-toluenesulfonate was prepared in the usual manner and recrystallized from pentane-ethyl acetate to give clusters of orange-yellow prisms, m.p. 46.2-47.2°.

Anal. Calcd. for $C_{21}H_{24}O_3FeS$: C, 61.17; H, 5.87; Fe, 13.54. Found: C, 61.12; H, 5.93; Fe, 13.37.

4-Ferrocenyl-1-butyl p-Bromobenzenesulfonate.--To 10.2 g. (0.040 mole) of 4-ferrocenylbutanol-1 dissolved in 100 ml. of pyridine and stirred in an ice-salt bath at 0° was added 10.0 g. (0.040 mole) of p-bromobenzenesulfonyl chloride in approximately 2 g. portions. The reaction mixture was stirred for three hours in the cooling bath, then an additional 3.0 g. of sulfonyl chloride was added, and the stirring was continued for an additional half hour. The reaction mixture was poured into 250 ml. of ice-cold 2N sulfuric acid, and then washed with water until the washings were neutral to Hydrion paper. The crude air-dried material (14.2 g., 74%) was recrystallized from ethyl acetate containing a few per cent of heptane, m.p. 85-86.5°. Recrystallization from cyclohexane gave orange crystals with a constant melting point, m.p. 86-87°.

Anal. Calcd for $C_{20}H_{21}O_3BrFeS$: C, 50.33; H, 4.44; Br, 16.75; Fe, 11.70. Found: C, 50.29, 51.33; H, 4.51, 4.44; Br, 16.43; Fe, 11.93, 11.94.

Glutaric Anhydride.--The procedure for the preparation of glutaric anhydride was as previously described for -methylglutaric anhydride (98). The product was distilled at 121-122°/3 mm., 24 g., 89% yield, m.p. 53-56°.

4-Ferrocenoylbutyric Acid.--An 80% yield of 4-ferrocenoylbutyric acid was obtained as previously described (96), m.p. 135-136.5°.

Methyl 5-Ferrocenylpentanoate.--To a stirred mixture of 530 g. of zinc, 600 ml. of water, and 25 ml. of conc. hydrochloric acid was added 40 g. of mercuric acetate. After stirring five minutes, the liquid was pipetted from the amalgamated zinc which was then washed with 500 ml. of water. Next 500 ml. of methanol, 500 ml. of conc. hydrochloric acid, and 50 g. (0.167 mole) of 4-ferrocenoylbutyric acid in 50 ml. of methanol (plus 50 ml. of methanol to wash in the keto acid) were added with stirring. The stirred mixture was maintained at reflux for 14 hours at the end of which time an aliquot removed from the reaction mixture and worked up exhibited no carbonyl absorption in the infrared, so the reduction was judged complete. The mixture was cooled to room temperature, decanted from the metal and extracted with methylene chloride in portions until the extract was colorless. The extract was washed with water until the washings were neutral to indicator paper and was dried over anhydrous magnesium sulfate. The filtered solution was concentrated to about 100 ml. by distillation under reduced pressure, 70 ml. of pentane was added, and the solution was chromatographed on 1000 g. of acid-washed alumina (Merck). Development with pentane and ether-pentane gave three bands: a small first band which was eluted with 10% ether-pentane and discarded; one large intermediate band which was eluted with 2 l. of 15% ether-pentane and 4 l. of 20% ether-pentane; and a small third trailing band. The solvent was distilled from the solution containing the second band under reduced pressure leaving a crystalline solid, 33.4 g., 67%, m.p. 39-40°. The infrared spectrum showed a single carbonyl at 1743 cm^{-1}.

5-Ferrocenylpentanol-1.--A solution of 30.0 g. (0.10 mole) of methyl 5-ferrocenylpentanoate in 160 ml. of anhydrous ether was added over a period of forty minutes to a stirred slurry of 3.8 g. (0.10 mole) of lithium aluminum hydride in 150 ml. of anhydrous ether. The mixture was stirred at room temperature for an additional forty minutes. The excess lithium aluminum hydride was decomposed with a solution of 10 ml. of ethyl acetate in 20 ml. of ether added dropwise to the stirred reaction mixture cooled in an ice-salt bath, and then 20 ml. of water followed by 80 ml. of 6N hydrochloric acid was added with stirring. The layers were separated, and the aqueous layer was extracted with three 50 ml. portions of ether. All ether solutions were combined, dried over barium oxide under an atmosphere of nitrogen in the refrigerator, and filtered. The solvent was distilled from the filtrate under reduced pressure. A brown liquid, 5-ferrocenylpentanol-1, was obtained, 26.5 g., 94%.

5-Ferrocenyl-1-pentyl p-Bromobenzenesulfonate.--To a stirred solution of 8.1 g. (0.03 mole) of 5-ferrocenylpentanol-1 in 80 ml. of dry pyridine cooled to -5° was added in portions during five minutes 10.0 g. (0.039 mole) of p-bromobenzenesulfonyl chloride. The cooled mixture was stirred one hour, then an additional 5.0 g. (0.02 mole) of the sulfonyl chloride was added, and the stirring was continued for three more hours. At the end of this time the mixture was poured onto ice and 500 ml. of cold 2N sulfuric acid. The yellow-tan precipitate formed was collected by suction, washed repeatedly with water, and air-dried, 14.2 g., 98%. Recrystallization from hexane containing a little benzene gave crystals, m.p. 105.8-106.4°. A second recrystallization did not change the melting point. A second crop was obtained from the mother liquors, m.p. 104.5-106.0°. This material together with some of the crude product was recrystallized from ethyl acetate, m.p. 106.2-107.0°.

Anal. Calcd. for $C_{21}H_{23}O_3BrFeS$: C, 51.35; H, 4.72; Fe, 11.37. Found: C, 51.57; H, 4.58; Fe, 11.15.

<u>Acetolysis Procedure</u>.--Since oxidation and decomposition of the ω-ferrocenyl-1-alkyl derivatives occurs readily at high temperatures and interferes with kinetic studies by consuming acid, it is necessary to carry out solvolyses in an atmosphere free of oxygen and in deoxygenated solvents. A sealed ampule technique and the use of various antioxidants were found not to be completely effective. Best results were obtained when a slow stream of oxygen-free dry nitrogen saturated with solvent vapor was bubbled through the solvolyzing mixture throughout a run with no antioxidants present. Even then, it was difficult to follow a reaction to greater than 50% completion. Since a meaningful infinity titer could not be obtained, it was necessary to use the theoretical infinity titer calculated from initial concentrations in order to determine the rate constants.

Anhydrous acetic acid was prepared by heating at reflux for four hours or overnight ten volumes of glacial acetic acid (Baker's analytical reagent) mixed with one volume of acetic anhydride followed by fractionally distilling the solvent through a 90 cm. long column packed with glass Raschig rings. The solvent was deoxygenated by bubbling a stream of oxygen-free dry nitrogen through it for a half hour before making up solfonate ester solutions.

A weighed quantity of ω-ferrocenyl-1-alkyl sulfonate was dissolved in the solvent, sometimes by warming, and the solution was made up to volume in a volumetric flask at 25°. Oxygen-free dry nitrogen was bubbled through the solution, and the volumetric flask was immersed in an oil bath maintained thermostatically at 103.8°. At intervals of time approximately 10 ml. aliquots were removed and the reaction quenched by delivery of the aliquot into an Erlenmeyer flask cooled in ice. The solution was brought to room temperature, and a 5.00 ml. aliquot was pipetted into about 50 ml. of stirred acetic anhydride. The liberated sulfonic acid was titrated potentiometrically with standard sodium acetate in glacial acetic acid which was about 1% in acetic anhydride. Plotting of the results according to the first order law gave good fits (straight lines).

Product Analysis of the Acetolysis of 4-Ferrocenyl-1-butyl *p*-Bromobenzenesulfonate.---A 0.04166 M solution of 4-ferrocenyl-1-butyl *p*-bromobenzenesulfonate in anhydrous acetic acid was maintained at 103.8° for one day. The reaction was stopped by cooling, then 25 ml. of this solution was pipetted into 200 ml. of water, and the mixture was extracted three times with 80 ml. portions of ether until the extract was colorless. The combined ether extracts were washed with 100 ml. of saturated sodium chloride solution, 100 ml. of 20% sodium carbonate solution, and

100 ml. of water and dried over anhydrous magnesium sulfate. The mixture was filtered and the ether was distilled to give a liquid residue, 0.315 g. The residue was dissolved in a few ml. of methylene chloride to which distilled ligroin (b.p. 30-60°) was added dropwise until the solution became cloudy. The solution was chromatographed on 22 g. of acid-washed alumina packed in distilled ligroin to give two bands. The first small band was eluted with ligroin and contained 0.018 g. of an oil. The infrared and ultraviolet spectra indicated that this material was probably a hydrocarbon. The ultraviolet spectrum measured in cyclohexane at a concentration of 13.9 mg./l. showed only end absorption. In the visible region there was adsorption at 420 mμ. The second band was eluted with 15% and 20% ether-ligroin and contained 0.192 g. of a liquid residue the infrared spectrum of which was identical to that of 4-ferrocenyl-1-butyl acetate.

Product Analysis of the Acetolysis of 5-Ferrocenyl-1-pentyl p-Bromobenzenesulfonate.--5-Ferrocenyl-1-pentyl p-bromobenzenesulfonate (2.47 g.) was dissolved in 100 ml. of anhydrous acetic acid. Oxygen-free nitrogen was bubbled through the reaction mixture maintained at 104° for 18 hours. The mixture, concentrated by volatilization of the solvent during the reaction period, was poured into 50 ml. of water. The mixture was extracted several times with ether, the ether solutions washed with water, dried over anhydrous sodium carbonate, filtered, and the ether distilled. The residue was dissolved in 15 ml. of methylene chloride and chromatographed on 80 g. of alumina packed in pentane. Elution with ether-pentane mixtures gave 1.29 g. of acetate ester identified by its infrared spectrum and 0.21 g. of a more polar substance, possibly acetylated ferrocenylpentyl acetate. No hydrocarbon was found.

Hydrolysis of 4-Ferrocentyl-1-butyl p-Bromobenzenesulfonate in "80%" Acetone-water.---4-Phenyl-1-butyl p-bromobenzenesulfonate and 4-ferrocenyl-1-butyl p-bromobenzensulfonate were solvolyzed in "80%" acetone-water at 50.0° ± 0.5°. The solvent was made up at room temperature (69° F.) from 50.0 ml. of boiled distilled water and 250.0 ml. of Baker's reagent grade acetone. No oxidation of the ferrocene derivative was observed. The acid liberated was titrated with sodium hydroxide to a phenolphthalein end point. Good first order plots were obtained.

TABLE X

Rate Data for Typical Acetolysis of 5-Ferrocenyl-1-pentyl p-Bromobenzenesulfonate at 103.8°

Titration	ml. base	Time, min.
1	0.23	15
2	0.84	60
3	1.13	90
4	1.60	135
5	2.08	180
6	2.82	240
7	3.72	300
8	4.28	360
9	5.07	450

Infinity titer, 10.79 ml.

% Completion, 47%

Rate constant, 2.39×10^{-5} sec^{-1}.

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II.

STEREOCHEMISTRY OF HALOGEN ADDITION TO 4-*t*-BUTYLCYCLOHEXENE

1. INTRODUCTION

Although electrophilic additions to carbon-carbon double bonds form a class of long known and well studied reactions, certain details of their intimate stereochemistry have not been investigated. In particular, it might have been argued on the basis of simple theoretical considerations (1, 2) that electrophilic addition to a rigid cyclic olefin would necessitate the new groups to be introduced into axial positions. However, adequate experimental evidence bearing on this point was lacking, and it was felt that an alternate more sophisticated theory was attractive and predicted less rigid results. It was with the desire to decide between these two alternate theories that the present study of the halogenation of 4-t-butylcyclohexene was undertaken.

1.1 Mechanistic Background for Stereochemical Studies

In order to describe more fully the stereochemical problem and understand its relation to the reaction mechanism, mechanisms of electrophilic addition to carbon-carbon double bonds will be briefly reviewed. Studies of products and product stereochemistry, kinetics, isotopic exchange, solvent effects on rates and products, and isotopic effects have led to the formulation of reasonably complete mechanisms of addition. It is convenient to separate additions into categories depending on the nature of the reagent and the polarity of the solvent in which the reaction occurs.

1.1.1 Solvent Effects

Changes in solvent may demonstrate an influence of solvent properties upon the outcome and, therefore, the mechanism of a reaction.* This influence is usually attributed to solvent polarity, by which is generally meant the combined electrostatic effects of the dielectric constant and dipole moments of solvent molecules, the effects of hydrogen bonding, more specifically oriented weak solvent bonding, etc. The noteworthy point is that the mechanism of a reaction may be altered by a change in solvent (5, 6). The rate of a reaction may also be changed since the ground states of reactants and transition states may be affected differently by solvent changes. In polar solvents the intermediacy of ionic species and ionic transition states is likely due to electrostatic stabilization of charge separation by solvation, whereas in non-polar solvents the smallest necessary charge separation in the transition state will generally reduce the free energy of activation, and similarly a minimum of ionic character will be possessed by any intermediates (7, 8). In mixed solvents, the more polar solvent molecules may become bunched about an ionic intermediate to the exclusion from the reaction site of less polar solvent molecules, and, indeed, polar reagents in non-polar solvents such as hydrogen chloride in pentane may cluster together (7, 8, 9).

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*Cf. references 3 and 4 for attempts at correlating and explaining solvent effects on rate.

Important to this study is the fact that the mechanistic changes, which occur in addition to rate changes when the solvent is varied, may frequently be reflected in the stereochemistry and especially the stereoselectivity of a reaction. This is partially due to the fact that in more ionizing solvents intermediates may have half lives long compared with inversion half lives.

1.1.2 Addition of Unsymmetrical Reagents

The general mechanisms of electrophilic addition of unsymmetrical reagents to carbon-carbon double bonds in the two extreme solvent cases will be discussed. By unsymmetrical reagent is meant a reagent adding different functional groups to each side of a given double bond. Such reagents might be hydrogen chloride or water in the presence of hydrogen ion.

1.1.2.1 Addition of Unsymmetrical Reagents in Polar Solvents

The hydration of olefins is an excellent example of unsymmetrical addition in a polar solvent and has been particularly well studied. Kinetic studies were performed early by Lucas and coworkers (10, 11, 12) and more recently by Ciapetta and Kilpatrick (13) and Taft, Hammett, and coworkers (14). The reaction is first-order in olefin and first-order in hydrogen ion.

A mechanism involving ionic intermediates is suggested for electrophilic addition in polar solvents (14, 15, 16). A simple version of the mechanism is depicted in figure 1. A fast equilibrium may exist between the olefin and the electrophile to produce the intermediate III as shown in figure 2. This intermediate is a π-complex in which the binding between the electrophile and the π-bond is generally considered to be weak. The electrophile causes only a slight perturbation of the π-bond while the carbon skeleton remains undisturbed. A distinction is made between a π-complex and bridged ions such as IV and V (fig. 3) (17), this distinction being primarily a difference in strength of the bonding of the bridging group to the double bond. Evidence for the π-complex III in electrophilic addition is meager and only suggestive.

Opening of III to give II (equation 4, fig. 2) would be expected to give predominantly the most stable carbonium ion which would lead to the products in accordance with Markownikoff's rule (18, 19). Rather than forming open carbonium ions such as II, collapse of III or direct electrophile attack may produce bridged intermediates such as IV and V, especially in additions of 1-alkylethylenes and 1,2-dialkylethylenes where bridging may help reduce the free energy of the carbonium ion (20, 21). The carbonium ion IV is symmetrically bridged whereas in V one of the carbon-electrophile bonds is nearly full strength, and configurational holding is still accomplished through weak bonding of the electrophile with the other carbon (22, 23).

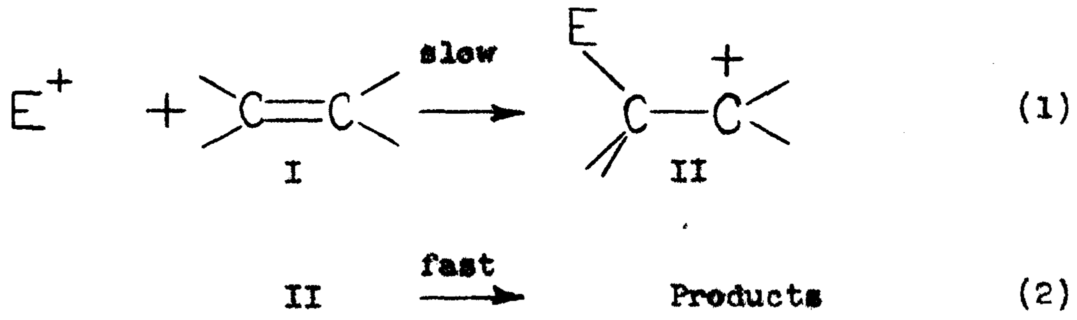

Figure 1.

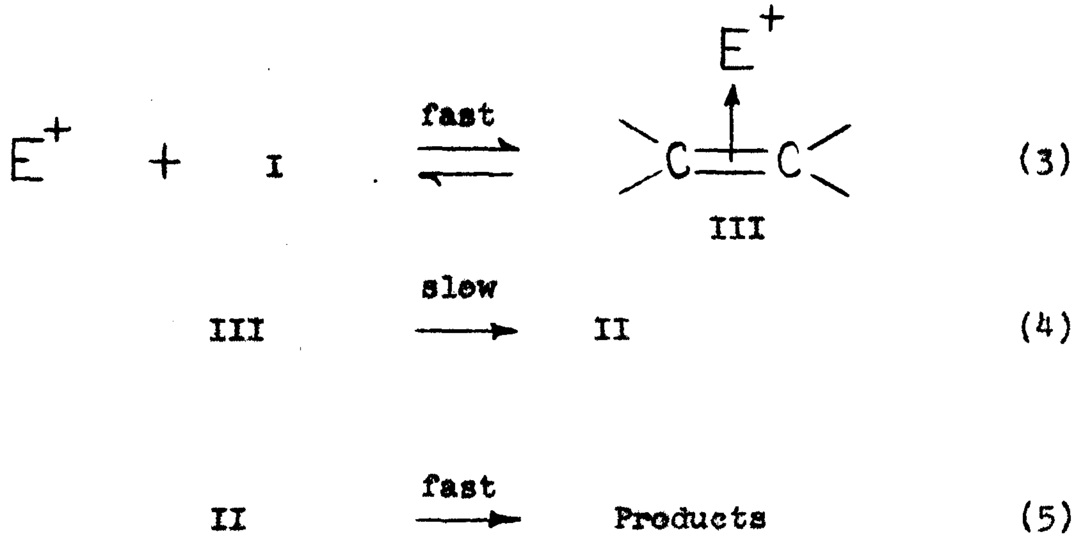

Figure 2.

IV V

Figure 3.

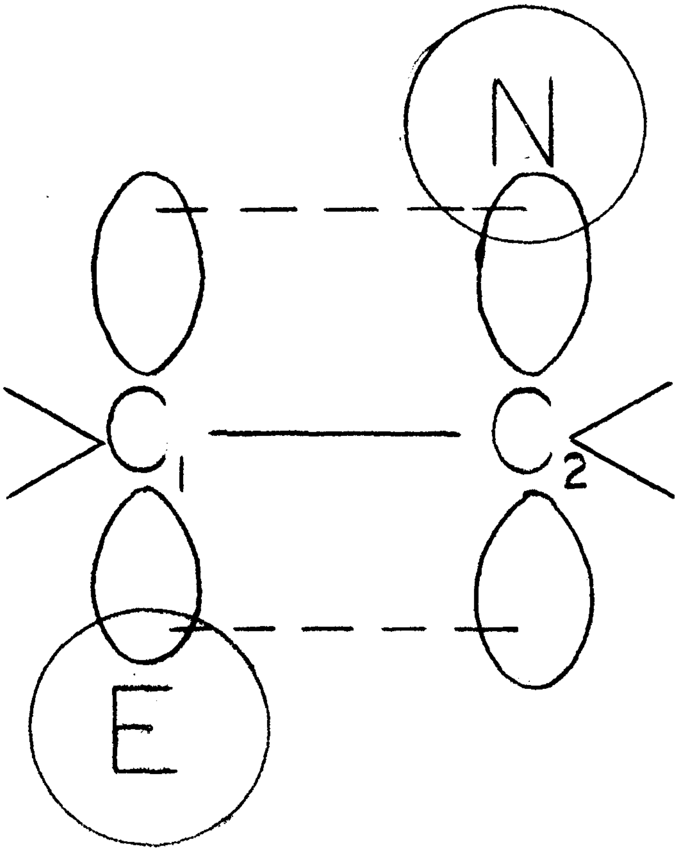

Figure 4.

Such intermediates are also possible if strain in a tertiary carbonium ion can be relieved by bridging. This could occur only in addition to specially constituted olefins.*

1.1.2.2 Addition of Unsymmetrical Reagents in Non-Polar Solvents

The kinetics of hydrogen chloride addition to isobutylene and hydrogen bromide to propylene in heptane are first-order in olefin and indefinite high-order in hydrogen halide (26, 27) as would be expected if the polar addendum forms a polymer in the non-polar solvent.

1.1.3 Halogen Addition

The mechanisms discussed in the previous sections were those for unsymmetrical reagents. Whether to expect the same mechanisms to apply to halogen addition in various solvents is still an open question since extensive studies comparable to, say, olefin hydration are not available. However, one would expect some of the distinctions made for unsymmetrical addition to hold for the halogens.

In polar solvents such as methanol or water (28, 29), addition of bromine or chlorine is first-order in halogen and first-order in olefin (30, 31). In addition to 1,2-dihalides, other products are obtained in nucleophilic solvents or in the presence of nucleophiles such as halide ions. This as well as other evidence (32) implies carbonium

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*For an example, see references 24 and 25.

ion intermediates. A basic mechanism similar to that of figure 1 will be assumed in this work. The basic mechanism must be modified in the presence of halide ions since it has been found that chloride ion may catalyze bromine addition, and the kinetics are actually first-order in each of olefin, bromine, and chloride ion (33). Even in solvents which are usually considered polar, complications may arise. For example bromine, iodine, or mixed halogen addition become second-order in halogen in the solvents acetic acid and nitrobenzene (34-37). Raising the polarity of the solvent by addition of water (37), lowering the bromine concentration (36, 37), or increasing the temperature results in a shift to first-order in bromine. To summarize, it appears that the electrophile in the case of bromine addition may be a bromine complexed with another bromine or in the presence of halide ions may be a complex of bromine and halide ion. The complexing becomes more pronounced in less polar solvents. In the case of chlorine such complexes are of less importance probably because chlorine is less polarizable than bromide. However, addition of chlorine in carbon tetrachloride may be catalyzed by iodine.

1.2 Stereochemistry of Electrophilic Addition

Analogous to *trans*-1,2-eliminations (38, 39, 40) it has generally been accepted that planar *trans*-addition is the usual and preferred course of electrophilic addition to double bonds (1, 41), at least in non-polar solvents where stereoselectivity is least likely to be lost (8).

Although radical <u>cis</u>-addition has been found (42-45), electrophilic <u>cis</u>-addition has not been observed although workers have been aware of this possibility (7). In general, the stereochemical outcome of an electrophilic addition to an olefin will depend on a number of factors among which the most important are probably the structure of the olefin, the electrophile, the nucleophile, and the solvent.

1.2.1 Previous Ideas Concerning Addition to Rigid Systems

For additions in non-polar solvents, at least, the usual hypothesis is that the entering groups, the electrophile and nucleophile, must lie <u>anti</u> to each other in the transition state and be as closely perpendicular to the nodal plane of the originally unperturbed π-orbital as is possible (fig. 4). The simple picture would involve simultaneous attack by electrophile and nucleophile from opposite sides of the carbon π-bond plane which is substantiated by the work of Hammond and Nevitt (8). Such a geometrical arrangement of groups, i.e. the electrophile, C_1, C_2, and nucleophile all in a single plane, is supposed to allow maximum bond formation, i.e. maximum orbital overlap, as well as provide stabilization of the transition state through electron delocalization (resonance). In view of this, additions to rigid cyclohexene rings in non-polar solvents must give diaxial products (1) since these bonds conform to the above restrictions (fig. 5). The mode of *trans*-addition which would lead to diequatorial products must involve a non-planar arrangement of entering groups in the transition state and would according to the above reasoning be prohibited (fig. 6). Yet, it remains questionable as to what extent the above reasoning is valid and is prohibitive of diequatorial product formation. The hypothesis of planar *trans*-addition was tested by studies of addition to 4-*t*-butylcyclohexene. The amount of diequatorial products actually produced has been measured under varying conditions.

1.2.2 Previous Suggestive Work

Previous work suggested the possibility that planar *trans*-addition is not the only stereochemical course of addition. Thus, bromination of rigid cyclic ketones is known to go through the enol and often gives equatorial bromides (46, 47, 48). However, these results can hardly be considered anything but suggestive since enolization and ketonization of the bromoketone may produce an equilibrium mixture of bromoketones. Alt and Barton (49) have found that the addition of bromine or chlorine to 2-cholestene gives in each case two isomers, $2\beta, 3\alpha$-dihalocholestane (VI, fig. 7) and $2\alpha,3\beta$-dihalocholestane (VII, fig. 7) in ratios of 9/1 for bromination and 7/3 for

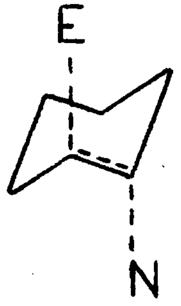


Figure 5.

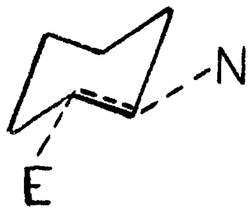


Figure 6.

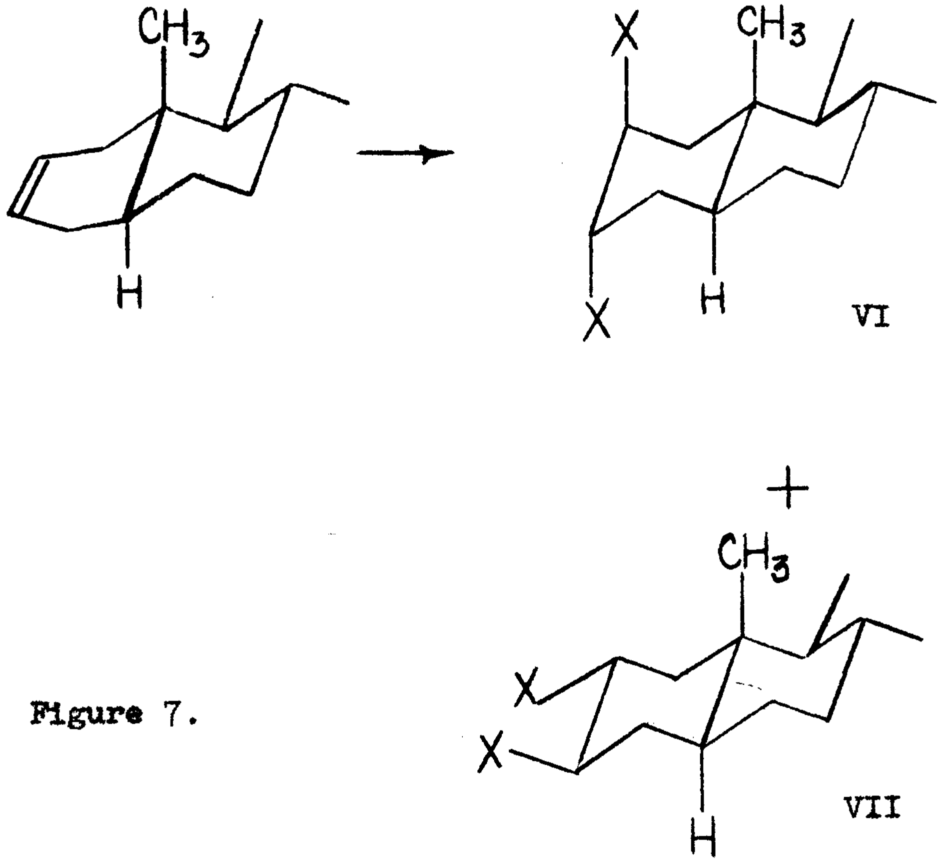
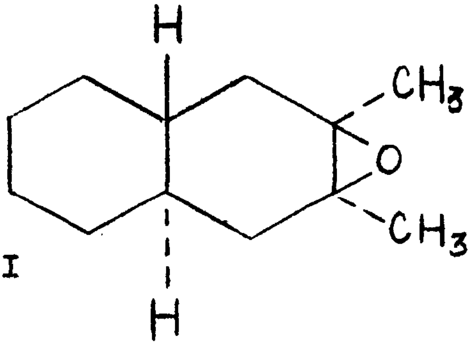


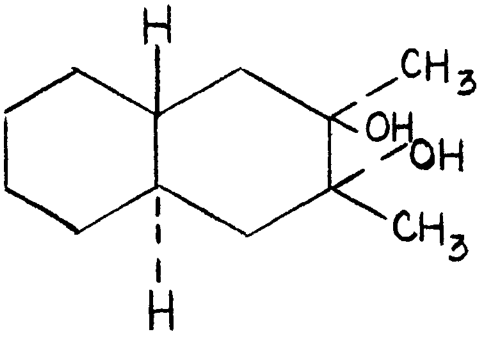
Figure 7.

chlorination. The diaxial dibromide VI (2β, 3α, isomer) did not isomerize to the more stable diequatorial dibromide during the work-up. It was not determined whether VI isomerizes under the reaction conditions to VII. Indeed, if this is the case, it is difficult to reconcile that the isomerization appears to be more facile for the diaxial dichloride than for the dibromide with the generally accepted idea that carbon-chlorine bonds are stronger than carbon-bromine bonds in displacement reactions in aliphatic systems. Addition of bromine to 3-cholestene in carbon tetrachloride gave only 3% of the diequatorial isomer in the mixture of dibromides obtained (49). An incomplete study of the addition of bromine to 4-_t_-butylcyclohexene showed that the reaction affords mixtures of the two possible epimeric _trans_-dibromides in which the diaxial dibromide predominated (50). The dibromide isomers were easily interconvertible, and, indeed, all of the above results in which some diequatorial products were obtained might be explained in terms of isomerization of initially formed diaxial products to diequatorial products since no experimental checks were made to eliminate this possibility. In the present work, the presence or absence of isomerization was examined.

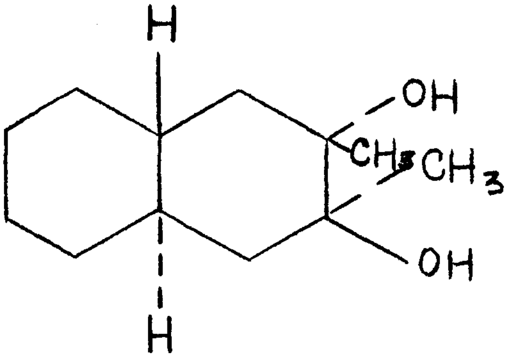
Another interesting result in connection with the formation of diequatorial products is the acid catalyzed opening of the epoxide (VIII, fig. 8) to give the _trans_-



VIII



IX



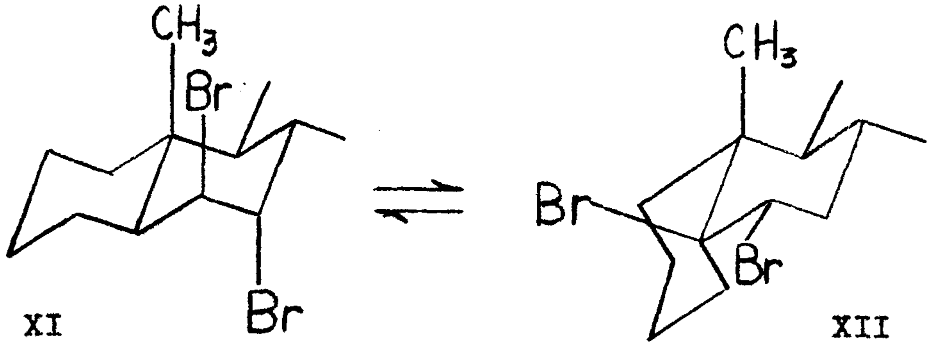
X

Figure 8.

diols IX and X in 71% and 23%, respectively (51). No *cis*-diols were isolated. The acid catalyzed opening of an epoxide is analogous to opening of a bridged carbonium ion. That 23% of the *trans*-diequatorial diol is produced is suggestive. However, here again the possibility that isomerization occurs is not excluded even though no *cis*-diols are formed, for neighboring hydroxyl participation may be sufficiently effective to hold configuration.

1.2.3 Isomerization of *trans*-1,2-Dihalides

In connection with the possible isomerizations of dihalides, $5\alpha,6\beta$-dibromocholestane (XI, fig. 9) is known to isomerize to $5\beta,6\alpha$-dibromocoprostane (XII) in a wide range of solvents of differing ionizing power (52). The rates increase with increasing solvent polarity. The kinetic and stereochemical results may be explained in terms of a bromonium-bromide intimate ion-pair for the rearrangements occurring in the more ionizing solvents. Less charge separation is supposed in less ionizing solvents. The rates of mutarotation were not affected by hydrogen bromide, catechol, or benzoyl peroxide in chloroform solution. However, catalysis of isomerization of XI in benzene by carboxylic acids and phenols has been observed (53). The authors have assumed this to mean general acid catalysis of isomerization. No increase in isomerization rate is produced by the addition of



XI XII

Figure 9.

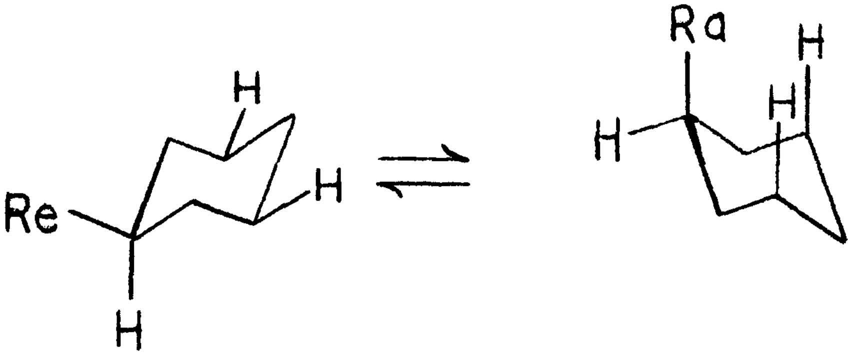
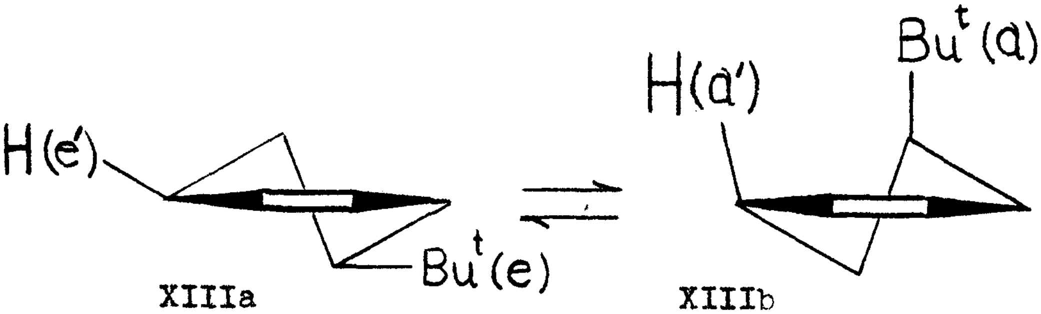


Figure 10.



XIIIa XIIIb

Figure 11.

piperidinium acetate which implies the absence of general base catalysis. The kinetic order with respect to carboxylic acids is unity whereas with phenols it is closer to two. The observation that a mixture of o-chlorophenol and phenol is about six times more effective catalytically than either phenol alone is reminiscent of the "termolecular" processes observed by Swain (54) and others (55).

Rate studies on the isomerization of some steroidal 5α,6β-dibromides were carried out by Barton and Head (56) who observed effects on rate due to polar groupings remote from the reaction center.

1.2.4 Interference of Radical Addition

The addition to olefins is often complicated by the occurrence, especially in non-polar solvents, of another mechanism in addition to electrophilic addition, namely free radical addition (57, 58). The simultaneous occurrence of radical addition will complicate any stereochemical interpretations since although free radical addition of hydrogen bromide to olefins is stereospecifically *trans* (59), halogen addition may be *cis* (42, 43, 60). Even though radical addition may be stereospecifically *trans* in a particular case, conformational selectivity may not be required; both diaxial and diequatorial *trans*-products might be formed. If radical addition is concurrent with electrophilic addition, any diequatorial products formed may arise through either or both processes. Care must therefore be taken to eliminate radical addition.

1.2.5 4-t-Butylcyclohexene as a Substrate for Electrophilic Additions

The 4-t-butylcyclohexyl system is nearly ideal for the study of electrophilic additions to double bonds. The products formed from addition to 4-t-butylcyclohexene (XIII) will have preferred conformations due to the large energy difference between an axial and an equatorial t-butyl group (fig. 10) (61-64). The olefin XIII, itself, undoubtedly has a more favorable conformation due to the "half chair" conformations of the cyclohexenyl system in which the bonds projecting from the ring retain much of the axial and equatorial character of the cyclohexyl system (fig. 11) (65). In 4-t-butylcyclohexene if the t-butyl group becomes axial it is opposed only by a single quasi-axial hydrogen, and the energy difference between an axial and equatorial t-butyl group in cyclohexene is thus smaller than in cyclohexane. Even so, the diaxial interaction between the t-butyl group and hydrogen should greatly favor XIIIa.

The t-butyl group is sufficiently removed from the double bond so as not to influence the addition while at the same time it holds the olefin in a fixed conformation. A test of the hypothesis that 4-t-butyl group exerts no influence on addition would result from a comparison of the products of unsymmetrical addition. The percentages of electrophilic attack at the 1- and 2-positions should be the same. It is well established that alkyl groups in the 4- and 3-positions in a cyclohexane ring exert no polar effect on reactions at the 1-position (61, 63, 66). It seems that any effects of the t-butyl group on additions to 4-t-butylcyclohexene may be ascribed to steric hindrance or buttressing effects (67). Effects due to ring deformation might also be operative (68, 69, 46).

2. RESULTS

4-t-Butylcyclohexene has been prepared previously from trans-4-t-butylcyclohexanol via the Chugaev elimination (61). In this work, it has been prepared cleanly in nearly quantitative yield by pyrolysis of 4-t-butylcyclohexyl acetate at 450°. An attempt to prepare the olefin by phosphoric acid catalyzed dehydration of the cis- and trans-4-t-butylcyclohexanols gave a mixture of olefin isomers.

Particular difficulties were encountered in following the bromination of 4-t-butylcyclohexene. Infrared analysis of the product mixture was not practical since one isomer was present in a relatively small amount. The column temperature required in order to get the dibromides through a vapor phase column in a reasonable time was sufficiently high to cause isomerization and equilibration of the two isomers. Several different types of absorbents were tried.

Finally, it was found that the α-hydrogens of the dibromides had different chemical shifts so that nuclear magnetic resonance spectra could be used for analysis. Bromination in benzene at 6° gave about 9% of the diequatorial dibromide, 1(e), 2(e)-dibromo-4(3)-t-butylcyclohexane. The ratio of isomers did not change measurably over a few hours. The relative amounts of each isomer were determined from the areas of peaks of the two kinds of α-hydrogens in the nuclear magnetic resonance spectrum.

The chlorination of 4-t-butylcyclohexene (XIII) was followed with much more ease than the bromination since the products did not isomerize readily. The two trans-1,2-dichlorides were distinguished on the basis of vapor phase chromatographic retention times, boiling points, equilibration experiments, and infrared spectra (70). The assignments of infrared stretching frequencies to axial and equatorial carbon-halogen bonds has been made previously (70). Table I lists pertinent data for 1,2-dichlorides. On the basis of these assignments, the infrared absorption band occurring at 740 cm^{-1} in the spectrum of the mixture of two dichlorides may be assigned to the equatorial C-Cl bond and the band at 683 cm^{-1} to the axial C-Cl bond (70). On heating a mixture containing 26% of the high boiling isomer (the isomer having the longest retention time) a mixture containing 16% of this isomer resulted. The infrared band

TABLE I

Infrared Stretching Frequencies for Dichlorides

compound	equatorial, Cl cm^{-1}	axial Cl cm^{-1}
$2\beta,3\alpha$-dichlorocholestane[a]	--	639
$2\alpha,3\beta$-dichlorocholestane[a]	784,738	
$5\alpha,6\beta$-dichlorocholestane[b]		652
trans-1,2-dichlorocyclohexane[c]	736,743	696
trans-1,2-dichlorocyclohexane[d]	738,746	692
cis-1,2-dichlorocyclohexane[e]	744[f]	696[f]
trans-1,4-dichlorocyclohexane[g]	724	688

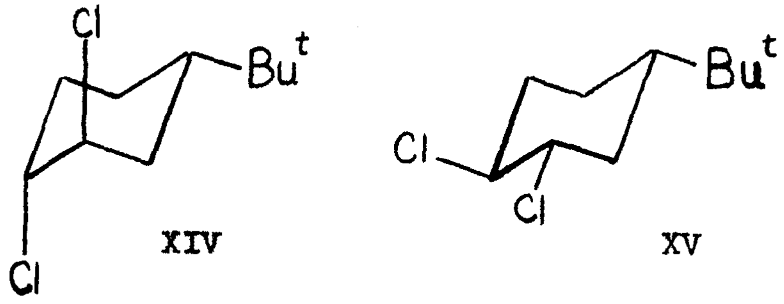
a) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284-4294 (1954); b) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, 72, 370-374 (1950); c) K. Kozima, K. Sakashita, and S. Maeda, *ibid.*, 76, 1965-1969 (1954); d) P. Klaeboe, J. J. Lothe, and K. Lunde, *Acta. Chem. Scand.*, 11, 1677-1691 (1957); e) K. Kozima and T. Yoshino, *J. Am. Chem. Soc.*, 75, 166-171 (1953); f) Raman spectrum.

occurring at 740 cm^{-1} relative to the 683 cm^{-1} band was reduced in intensity by about one-half. That no new compounds were formed in the isomerization is evidenced by the fact that no new bands appeared in the infrared spectrum and no new bands were found by vapor phase chromatography. The mixture of dichlorides probably contains but two major components since but two well separated peaks occurred on vapor phase chromatography on a variety of columns (silicone rubber, carbowax 1500, diisodecylphthalate). However, the presence of small quantities of other isomers (such as 1,3-dichlorides and 1,4-dichlorides) cannot be ruled out especially since some of these isomers may have polar properties similar to the 1,2-diequatorial dichloride and may not be separated easily by vapor phase chromatography. Additional support for the assignment of structures to the dichloride products comes from the behavior of the mixture upon distillation. The diequatorial isomer would have the highest boiling point (71) and the longest retention time since it has the largest dipole moment. It was established that the products were neither vinylic nor allylic chlorides by elemental analysis, infrared spectra, and independent synthesis of 1-chloro-4-t-butylcyclohexene and comparison of its retention time and infrared spectrum with the chlorination product mixture.

Chlorination of XIII in pentane at 0-6° gave a mixture of 74% of 1(a),2(a)-dichloro-4(e)-t-butylcyclohexane (XIV, fig. 12) and 26% of 1(e),2(e)-dichloro-4(e)-*t*-butylcyclohexane (XV). Furthermore, the ratio of XIV and XV remained constant throughout the reaction with a standard deviation of about 2% for the diequatorial isomer percentage. It was also established that XIV and XV were individually stable under the reaction conditions, i.e. no isomerization occurred, and a mixture originally containing 16% of XV was not changed by treatment with chlorine in pentane over a period of about two and one-half hours.

Free radical addition was suppressed by the presence of 2,6-di-*t*-butyl-*p*-cresol, although towards the end of the reaction period (after two hours) some of the pentane solvent was chlorinated. Later experiments showed that the presence of anthracene would prevent pentane chlorination. All reactions were shielded from light. Some hydrogen chloride was evolved.

Chlorination of XIII in benzene at 7° in the presence of anthracene gave 28% of XV. A small amount of hydrogen chloride was also evolved. Chlorination of XIII in chlorobenzene at 0-5° gave 41% of XV. The composition of the product mixture did not change during the forty minute reaction period. Again a small quantity of hydrogen chloride was evolved indicating some free radical substitution had occurred. At 15-17° in acetic acid, 70% to 75% of XV was formed among the dichloride products. Additional products, probably chloroacetates, were also formed. Treatment of a



XIV

XV

Figure 12.

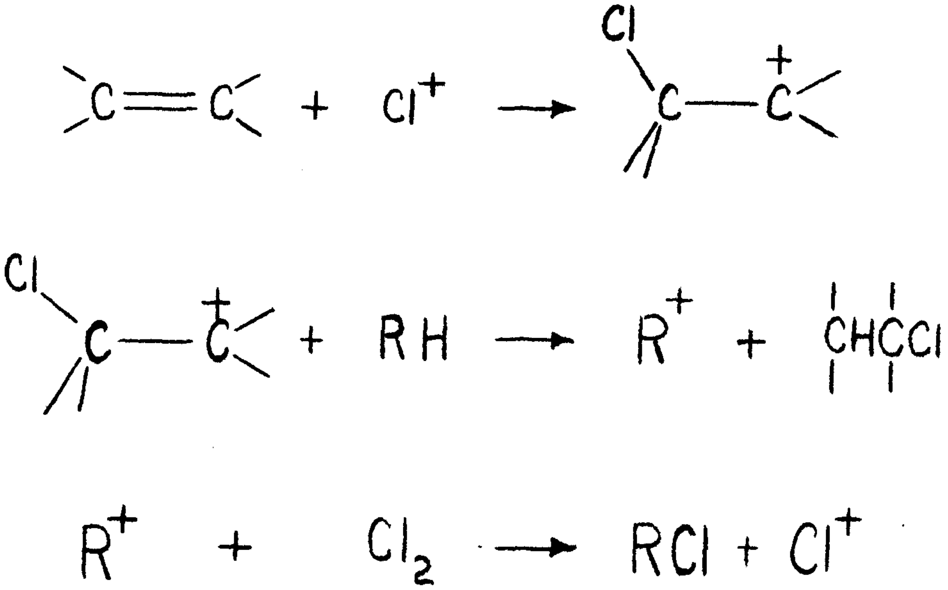


Figure 13.

mixture of dichlorides containing 32% of XV in acetic acid at room temperature for four hours caused isomerization to 41% of XV. Table II summarizes the chlorination results.

TABLE II

Chlorination of 4-*t*-Butylcyclohexene

Solvent	Temperature, °C	% XV
pentane	7°	26
benzene	7°	28
chlorobenzene	5°	41
acetic acid	15-17°	70-75

Cyclohexene, purified to remove hydroperoxides, was chlorinated in carbon tetrachloride. No allylic chlorides were produced unless the reaction was irradiated with light. In the presence of benzoyl peroxide a small amount of 3-chlorocyclohexene was formed in addition to 1,2-dichlorocyclohexane. Larger amounts of allylic chloride were not formed in this instance probably because the temperature was not favorable for the decomposition of benzoyl peroxide.

3. DISCUSSION

3.1 Occurrence of Free Radical Addition

The presence of free radical halogen addition as well as electrophilic halogen addition might compromise stereochemical interpretations of the mechanism of the electrophilic halogen addition. Radical addition could be clearly <u>trans</u> but may not be stereoselective for diaxial or diequatorial dihalide formation. Therefore, it is necessary to assess the extent of the occurrence of radical addition.

In all of experiments there probably occurred some radical addition since hydrogen halide was detected. The hydrogen halide probably results through allylic halogenation of the olefin. Its presence implies the presence of free radicals which might also add to the olefin. The amount of hydrogen halide was assessed in several cases. The amount formed did not constitute a significant fraction of the chlorine or bromine introduced into the reaction mixture (possibly a few per cent) thus making it unlikely that much of the reaction went by way of radical addition. Indeed, no allylic halides could be detected in the product mixture.

A further indication of the presence of radicals occurred in the addition to 4-t-butylcyclohexene in pentane. Although an antioxidant, namely 2,6-di-t-butyl-4-methylphenol, was present in the reaction mixture, chloropentanes were formed towards the end of the chlorine addition. Aliquots removed earlier from the addition reaction contained little, if any, chlorinated pentanes. No 3-t-butyl- or 4-t-butylcyclohexyl chlorides were found which would be expected to form from hydrogen chloride released in allylic chlorination and chlorination of pentane under radical conditions. It seems likely that chlorine atoms are not formed until excess chlorine is present, the olefin and inhibitor consumed in chlorination, and any dissolved oxygen dispelled. On the other hand, the above result may simply reflect the inefficiency of pentane compared to olefin or inhibitor as a radical trap.

Light was carefully excluded from the reaction vessels. However, no attempt was made to exclude atmospheric oxygen from the reaction mixture. Under the proper conditions, oxygen is a strong inhibitor of radical chlorination (72). In order to suppress radical addition, an efficient chlorine radical scavenger was desired. In some of the initial experiments, 2,6-di-t-butyl-4-methylphenol was present which may be expected to scavenge chlorine radicals. However, this expectation may not be correct since the phenol hypochlorite may be formed which might itself give rise to radicals. Anthracene was, therefore, investigated as a possible chlorine atom scavenger. Indeed, although benzene is unreactive towards $\cdot CCl_3$ radicals, anthracene retards the radical addition of bromotrichloromethane to styrene (73) and might do the same for chlorine addition.

The efficacy of anthracene for scavenging chlorine radicals was tested by chlorinating a solution of anthracene in 66% benzene - 33% pentane. This solvent mixture was necessary due to the limited solubility of anthracene in pure pentane. No chlorinated pentanes were formed. If the effect of benzene is neglected (75), this result implies that if the chlorinated pentanes were produced by a radical process, anthracene is a good scavenger, or, conversely, if anthracene is a radical scavenger the chloropentanes formed in the 4-_t_-butylcyclohexene chlorination were produced by a radical process.

An alternate possibility for the formation of chloropentanes is that they are produced by an electrophilic process requiring the participation of olefin in the reaction. The electrophile produced by reaction of Cl^+ with olefin may abstract a hydride from solvent to yield a carbonium ion which in turn would react with nucleophilic chloride ions to yield alkyl chlorides (fig. 13). A similar example of hydride abstraction catalyzed by aluminum halides has been reported by Bartlett, Condon, and Schneider (74). However, this possibility is unlikely in view of the absence of 3- or 4-_t_-butylcyclohexyl chlorides in the product mixture from 4-_t_-butylcyclohexene chlorination.

Several additional arguments may be summoned against the occurrence of radical addition. Anthracene was used in the chlorination in benzene yet diequatorial dichloride was still produced. In acetic acid solvent a large amount of this product was also produced. Since acetic acid is considerably more ionizing than benzene, the electrophilic addition reaction should be favored in acetic acid.

Although free radical addition of hydrogen bromide to olefins is stereospecifically *trans* (59), free radical addition of chlorine need not necessarily be so. There are examples of *cis*-radical addition (42, 60). Thus, if chlorine addition to 4-*t*-butylcyclohexene does not yield *cis*-products, *cis*-radical addition has not occurred.

The chlorination of 4-*t*-butylcyclohexene appears to be cleanly *trans* since but two products are formed which are readily interconvertible by heating. Also, in the analogous steroid case no *cis*-materials were formed (49).

Allylic halogenation has been mentioned as a reaction which occurs under free radical conditions (76). Thus, cyclohexene in carbon tetrachloride in the presence of peroxides yields allylic substitution products (76, 77). Chlorination of cyclohexene in carbon tetrachloride at low temperatures in the absence of light but in excess chlorine has been reported by Böhme and Schmitz (78) to give 3-chlorocyclohexene as well as *trans*-1,2-dichlorocyclohexene. These conditions are quite similar to those used in this work. The chlorination of cyclohexene was repeated with carefully purified cyclohexene. However, it was found that no 3-chlorocyclohexene was formed unless the reaction mixture was exposed to light. Perhaps the cyclohexene used by Böhme and Schmitz was not free of hydroperoxides or perhaps dehydrohalogenation occurred during the work-up. Since no allylic chlorides are formed, it appears that radical allylic chlorination is absent in the chlorination of cyclohexene and 4-t-butylcyclohexene in the absence of light. This implies that radical addition is also absent, at least in the initial stages of the reaction.

When two addition products were found from the halogenations of 4-t-butylcyclohexene, the possibility that the extra product (the product in addition to the trans diaxial dichloride) was 1-halocyclohexene was considered. This product might be formed as in figure 14. However, analytical results and infrared spectra as well as a comparison of the chlorination product with an authentic sample of 1-chloro-4-t-butylcyclohexene eliminated this possibility. 1-Chloro-4-t-butylcyclohexene may still be formed under more ionizing conditions such that intermediates bearing significant positive charge are formed and have reasonably long half lives. This vinyl chloride was not looked for in the chlorination carried out in acetic acid primarily due to the variety of products produced in this solvent which renders their separation and identification difficult.

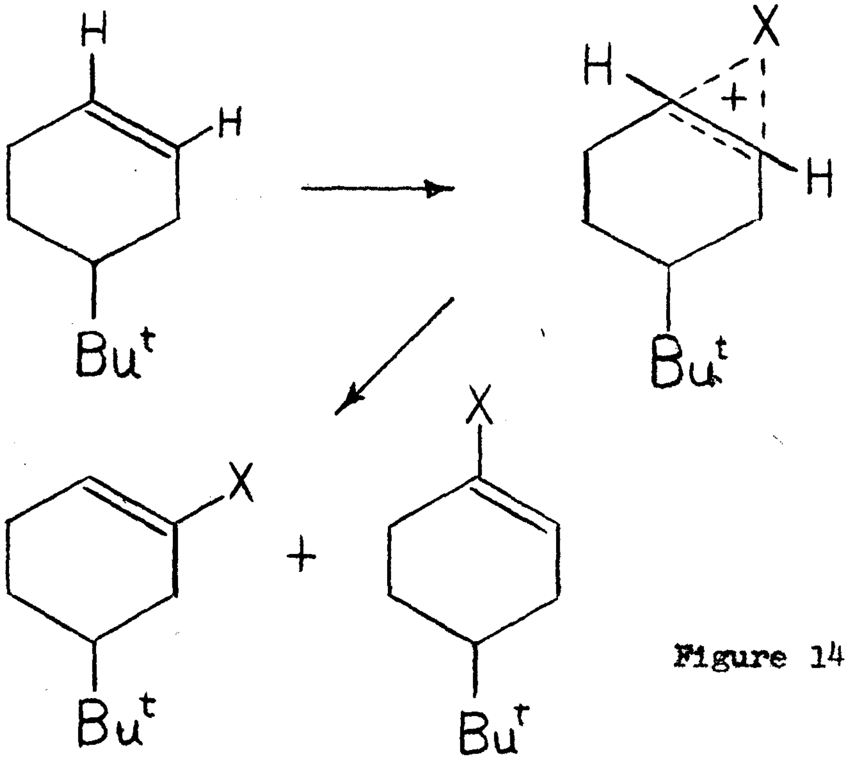


Figure 14.

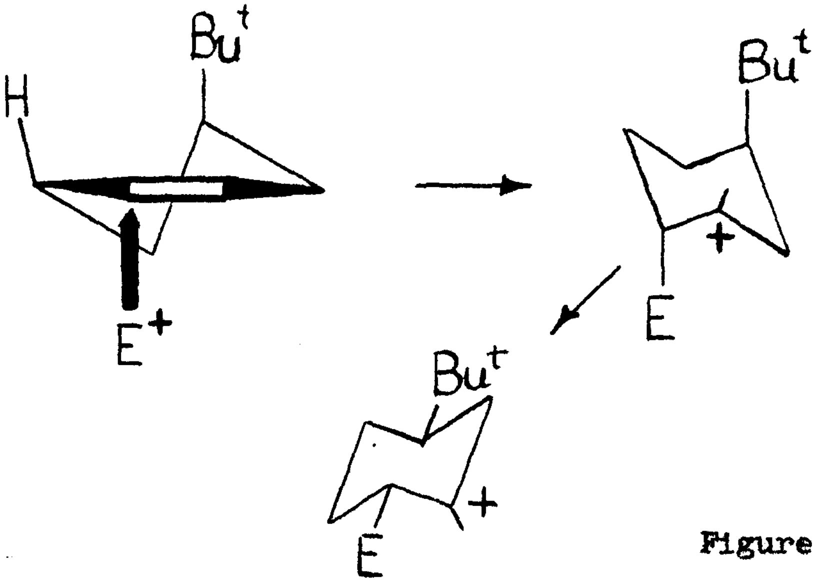


Figure 15.

3.2 Stability of the Dihalides Under the Reaction Conditions

A diaxial trans-1,2-dihalide may undergo isomerization to the diequatorial isomer under the proper conditions analogous to the isomerization of steroidal-5,6-dibromides which was discussed in the introduction. As a matter of fact, the rates of isomerization of the steroidal dibromides may be accelerated when compared to simple 1,2-dihalocyclohexanes due to 1,3-diaxial interaction of the 10-methyl and 6-bromide in 5α,6β-dibromocholestane. One might expect that 1(a), 2(a)-dibromo-4-t-butylcyclohexane would not be converted as readily to the diequatorial isomer. Even so, it has been observed that the dibromides are equilibrated on distillation (50), and in this work they were found to equilibrate on a gas chromatograph column. The 1,2-dichloro-4-t-butylcyclohexanes were found to be considerably more stable than the bromides so that chlorination could be more easily studied. Under the reaction conditions no measurable amount of isomerization of the dichlorides occurred except in acetic acid solvent. Even in acetic acid solvent the isomerization was not facile enough to account for more than a few per cent of XV. Furthermore, during a chlorination the ratio of XIV and XV remained constant which indicates that the mixture of isomers is formed directly from the addition reaction.

3.3 Influence of the t-Butyl Group

It was mentioned previously that the t-butyl group would not be expected to exert an influence upon electrophilic addition provided it remains in an equatorial position throughout the reaction. In order to test the influence of the t-butyl group on addition, acetic acid was added to 4-t-butylcyclohexene. The reaction was catalyzed by perchloric acid. Unfortunately, the interpretation of the results is complicated by the isomerization of the starting olefin to 3-t-butylcyclohexene and 4-t-butylcyclohexene, but reasonably comparable amounts of products are formed in the initial stages of the addition reaction. This result would support the contention that the t-butyl group does not exert an important electronic influence on the 3-position relative to the 4-position.

3.4 Mechanism and Stereochemistry

Electrophilic trans-addition to rigid cyclohexenyl systems may not necessarily give exclusively diaxial products as the experimental results show. There are several possible explanations which might account for the direct formation of diequatorial products. The t-butyl group of XIII may not always remain in a quasi-equatorial position in the olefin, a boat form of the olefin might be formed, or the addition may proceed so that the entering groups bend away from the π-bond plane. Each of these explanations will be considered in turn.

The olefin XIII may be in conformational equilibrium as in figure 11 where the t-butyl group is quasi-equatorial in XIIIa and quasi-axial in XIIIb. This equilibrium would be important if the energy barrier is not too high (not greater than four or five kcal.), and if the energy of XIIIb is not too much greater than that of XIIIa. Indeed, the energy difference should be smaller than in the case of cyclohexane (fig. 10) since one of the axial hydrogens is removed in the olefin. One would not expect the equilibrium constant ever to be as great as unity, even though the case where it is not negligible must be considered. If one assumes the t-butyl group in a quasi-axial position, then it will block the approach of the electrophile to one side of the ring which restricts approach to the other side (fig. 15). Similarly, the nucleophile cannot approach the side opposite the electrophile until the ring system "flips" and the t-butyl group again becomes equatorial. The nucleophile may then approach from the least hindered side of the ring to give diequatorial product. This mechanism does not explain the diequatorial product obtained from addition to 2-cholestene (49) since in the steroid system the olefin cannot exist in conformational equilibrium.

The reaction might also proceed as in figure 16 where an intermediate boat form is developed in which the X-C-C-X bonds all lie in one plane. This process would seem unfavorable since one of the entering groups will be eclipsed

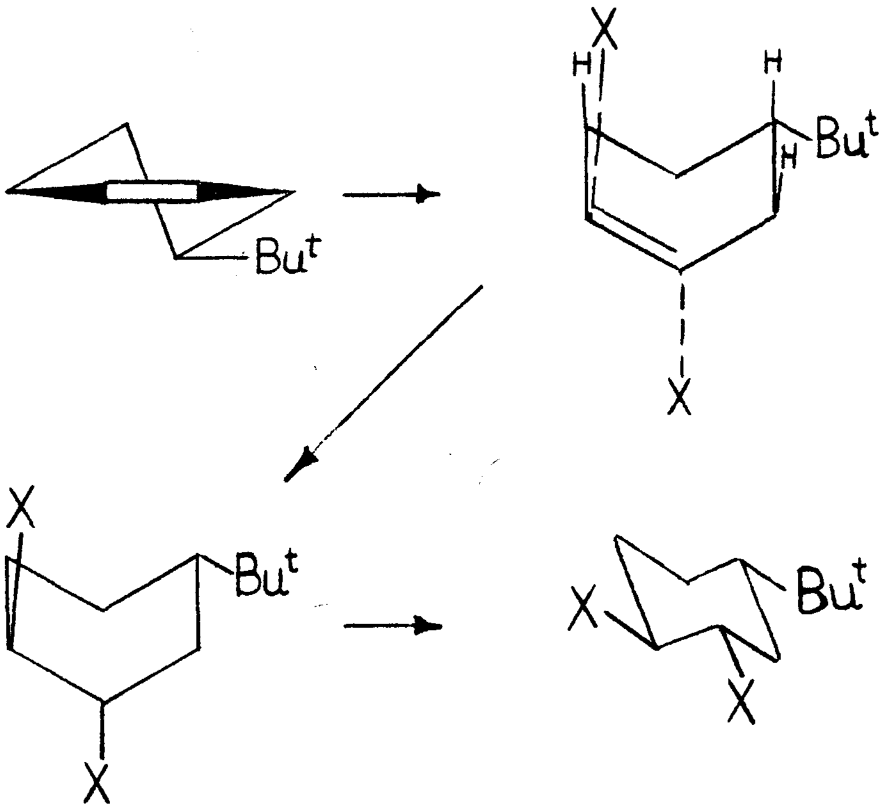


Figure 16.

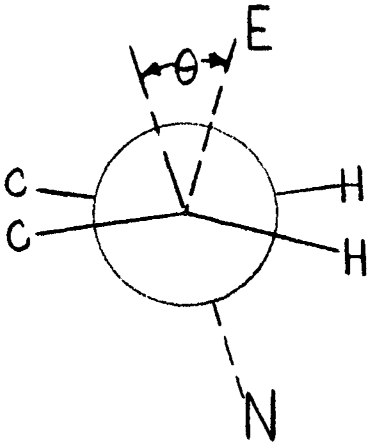


Figure 17.

by three axial hydrogens and the other group will be involved in a 1,4-interaction even though the boat form may be somewhat twisted to reduce these unfavorable interactions.

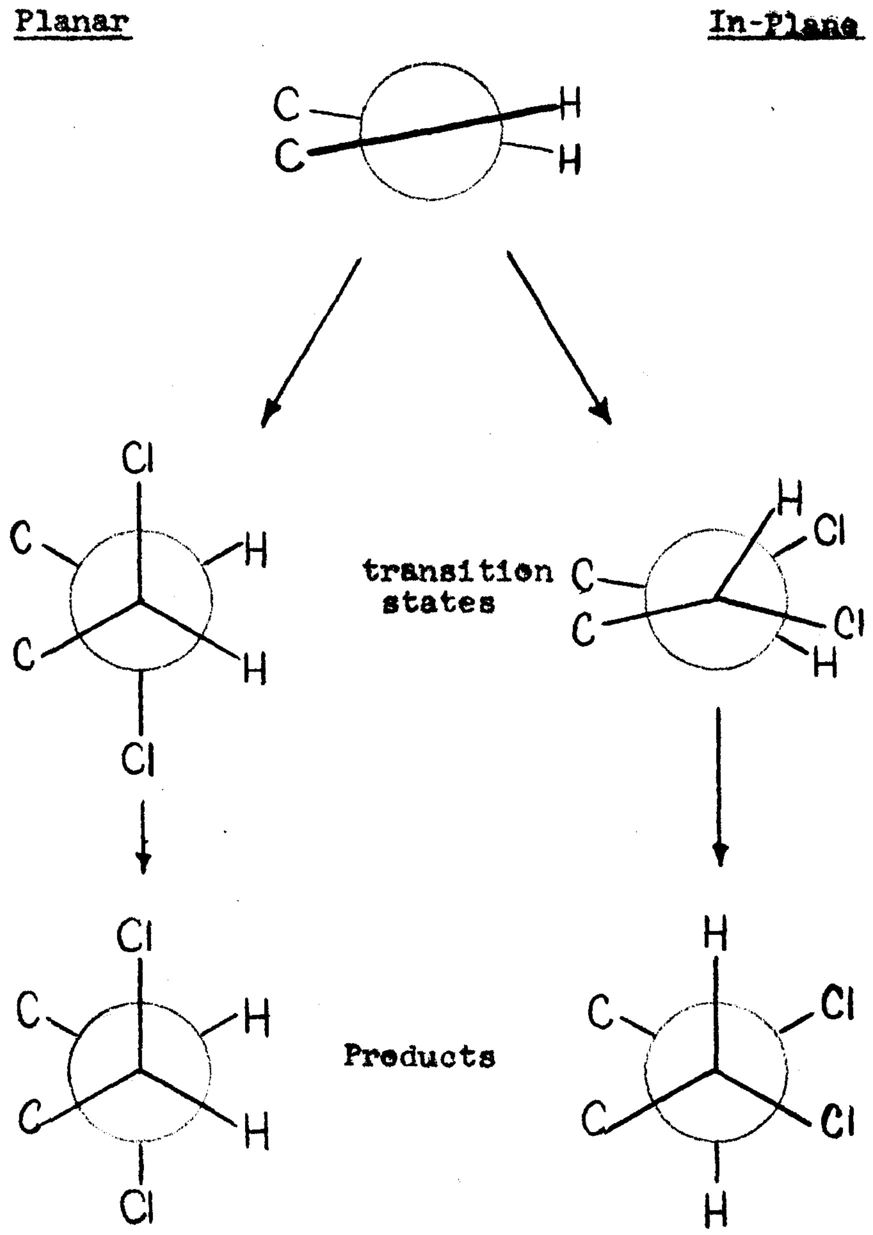
If maximum overlap in the double bond must be maintained, then the entering groups could not move away from the π-bond plane (see pg. 97). Although planar trans-addition appears to be the predominant mode of halogen addition in non-polar solvents, considerable amounts of diequatorial product are obtained which are probably not the result of planar trans-addition since explanations such as addition to 4-t-butylcyclohexene in the conformation with the bulky t-butyl group axial or addition going through a boat intermediate do not seem adequate.

One is, therefore, led to postulate an "in-plane" addition mechanism (7) operating concomitantly with planar trans-addition. In the in-plane addition mechanism, both entering groups may come from the same halogen molecule, and a minimum of charge separation is required. The entering groups may be bent away from the π-orbital plane in the transition state, i.e. the $E-C_1-C_2$ plane may make a dihedral angle with the C_1-C_2-N plane (fig. 17). Since the resonance energy of a normal π-bond varies as the $\cos^2\theta$, where θ is the angle of twist (79), a dihedral angle of 18.5° means a loss of only 10% of the resonance energy. If the π-bond undergoing addition is assumed to be a perturbed normal π-bond, a similar functional dependence of resonance energy on twist angle is quite likely. The minimization of charge separation may overcome any energy lost due to twisting of the π-bond. A simplified version of the combined mechanisms, planar trans-addition and in-plane trans-addition, is shown in figure 18.

The in-plane mechanism allows the E-C and the N-C bonds to be formed simultaneously. The addition of hydrogen bromide to the 1,2-dimethylcyclohexenyl system seems to involve the simultaneous formation of the C-H and C-Br bonds (8), and such may be the case for chlorine addition.

Table I shows that there is a strong dependence of the product distribution for chlorination of XIII on the solvent. As the solvent polarity increases so does the amount of diequatorial product. The dielectric constant of the solvent increases in the same order as the increase in diequatorial product (Table III) although a straight line relationship between dielectric constant and the product ratio or the log of the product ratio does not exist. Acetic acid provides the opportunity for hydrogen bonding which possibility is absent in the other solvents.

As the solvent polarity increases more diequatorial product is obtained, and, thus, more in-plane addition might be said to have occurred. However, the in-plane mechanism may be expected to be favored when charge


Planar
In-Plane
C
C
H
H
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H
C
H
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transition states
C
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H
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Cl
H
Cl
C
H
C
H
Cl
Products
H
C
Cl
C
Cl
H

Figure 18.

TABLE III

Dielectric Constants at 20° (80)

Solvent	D	% XV
pentane*	1.9	26
benzene	2.28	28
chlorobenzene	5.65	41
acetic acid	6.17	70-75

*The dielectric constant of pentane was estimated from the data available for other hydrocarbons such as hexane.

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separation must be reduced, as is required in non-polar solvents. Thus, the in-plane mechanism does not explain the observed effect of solvent on the reaction products.

Another mechanistic explanation is possible. In particular, a bridged halonium ion may open or a π-complex may collapse to place the halo group in an equatorial position. The nucleophile may then attack the carbonium ion center to yield diequatorial <u>trans</u>-product (fig. 19). If all the interaction of the halogen atom with the carbonium ion center in XVIIa and XVIIb is lost, then it is difficult to explain the absence of <u>cis</u>-addition. Steric hindrance due to the axial hydrogens at the 3 and 5 positions in XVIIa and the 4 and 6 positions in XVIIb favors the formation of diequatorial products from these intermediates. Some small

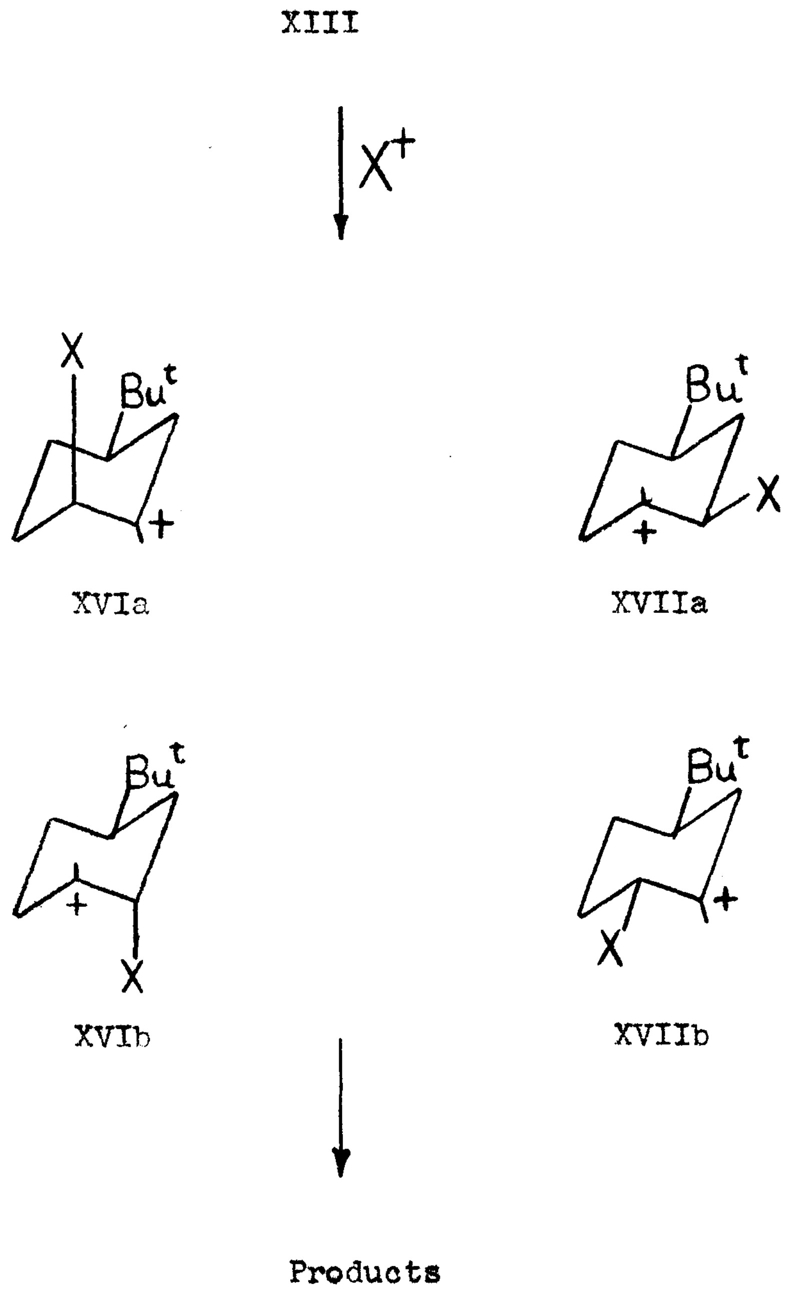

Figure 19.

interaction between the adjacent halogen and the carbonium ion may be all that is necessary to hold configuration (16).

The formation of both diaxial and diequatorial products as well as the behavior of the reaction in various solvents is explained by the operation of a carbonium ion mechanism which leads to diequatorial product and the conventional trans-addition mechanism which gives the diaxial products. As the solvent polarity increases the carbonium ion mechanism leading to diequatorial products is favored and eventually predominates.

Bromine is a good bridging group (81, 82, 83), and the bromonium ion would be expected to be attacked directly without previous opening to allow the bromine to move to an equatorial position.. It is difficult to reconcile the fact that the bromine addition produces as much diequatorial product as is found (9% from bromination of 4-t-butylcyclohexene). It is possible that the diequatorial dibromide was formed by isomerization of diaxial dibromide. More experimental work needs to be done on the addition of bromine to olefins and on the stereochemistry of the opening of bromonium ions in rigid cyclic systems. If it turns out that diequatorial dibromides are formed directly in addition, then perhaps a third mechanism, namely in-plane attack, must be considered for the bromine case.

In summary electrophilic halogenation has been shown to produce appreciable amounts of diequatorial dihalide. For chlorination, the relative amount of diequatorial dichloride increases as solvent polarity increases. The most likely mechanistic explanation of these results involves the classical mechanism which leads to diaxial products together with a carbonium ion mechanism which is responsible for the formation of diequatorial products.

3.5 Rearrangements During Chlorination

If an open carbonium ion is formed, there is the possibility that it may eliminate or rearrange. An example of elimination occurring during chlorination is provided by the reaction of chlorine with isobutylene which leads to the production of methallyl chloride (84, 85). Evidence was advanced for the explanation of this result in terms of the formation of a chloromethyldimethylcarbonium ion which is followed by the loss of a proton from a methyl group adjacent to the carbonium ion center. Also, the chlorination of methylenecyclohexane produces 1-chloromethyl-1-chlorocyclohexane in 12-19% yield and the elimination product, 1-chloromethylcyclohexene, in 38-48% yield (86). These latter authors prefer to explain the formation of the allylic chloride in terms of a cyclic transition state in which the C-Cl bond and the hydrogen chloride are formed simultaneously.

Rearrangement of a carbonium ion is also known to occur in some electrophilic addition reactions. For example, the addition of dinitrogen pentoxide to cyclohexene yields a complex mixture of products among which are cis-1-nitro-2-cyclohexyl nitrate, trans-1-nitro-3-cyclohexyl nitrate, and olefinic products (87). These results suggest that nitration by nitronium ion is occurring. The migration of a hydrogen gives rise to the trans-1-nitro-3-cyclohexyl nitrate. The rearrangement of the initially formed nitrocarbonium ion to yield 1,3-substitution is probably facilitated by the presence of the nitro group dipole which interacts unfavorably with an adjacent carbonium ion.

For a properly constituted olefin, rearrangement may occur during chlorination. Schmerling found that the chlorination of norbornene in pentane at -75° gives two products (88). Roberts, Johnson, and Carboni demonstrated that these products are nortricyclyl chloride and syn-7-exo-2-dichloronorbornane which are produced in 43% and 37% yields, respectively (89). Nortricyclyl chloride results from a 1,3-elimination from the carbonium ion intermediate. The dichloride product, syn-7-exo-2-dichloronorbornane, is a result of a skeletal rearrangement.

Additional examples of rearrangement during chlorination may be found. The chlorination of α-pinene at 0° yields 2,6-dichlorocamphane (90, 91) via a 1,2-shift of the bridging dimethylmethylene group. Rearrangement may also occur in the chlorination of 3,3-dimethyl-1-butene as reported by Cook and Whitmore (92). Although 53% of the starting material is accounted for by the formation of 1,2-dichloro-3,3-dimethylbutane, 6% of a mixture of different chloroalkanes or chloroalkenes is also formed. This mixture was thought to contain mostly unsaturated dichlorides. It is also possible that the mixture is the result of a rearrangement of a chloromethyl-t-butylcarbonium ion followed by elimination or substitution.

If chlorination of 4-t-butylcyclohexene produces a carbonium ion which is sufficiently stable or long lived, or if driving forces for elimination or rearrangement exist, eliminated or rearranged products may be formed in addition to the expected 1,2-dichlorides. Elimination products have been shown to be absent since appropriate bands in the infrared spectrum of the chlorination product mixture are lacking.

The situation with regard to the occurrence of rearrangement during the chlorination of 4-t-butylcyclohexene is not clear. Formation and rearrangement of a carbonium ion formed in the chlorination would produce 1,3-dichlorides and possibly 1,4-dichlorides. The actual results were as follows. Vapor phase chromatography of the chlorination product mixture gave only two peaks. Infrared spectral evidence indicated that both axial and equatorial C-Cl bonds were present.

Heating the product mixture produced an increase in the axial C-Cl bond concentration relative to the equatorial C-Cl bond concentration as indicated by both vapor phase chromatography and infrared spectral evidence. It is suggested that the original chlorination production mixture consisted primarily of 1,2-diaxial and 1,2-diequatorial dichlorides with the possibility that 1,3-dichlorides and 1,4-dichlorides are present in smaller amounts. This suggestion is based on the following considerations: i) the facile isomerization of a 1,3-dichloride having an equatorial C-Cl bond to the 1,3-diaxial dichloride is improbable due to the 1,3-diaxial interaction in the product; ii) the facile isomerization of a 1,3-dichloride to the 1,2-diaxial dichloride seems unlikely; iii) the 1,2-diequatorial dichloride should be formed with similar ease as is a 1,3-dichloride.

Since only two peaks were observed on vapor phase chromatography of the chlorination product mixture, the retention times of any 1,3-dichlorides or 1,4-dichlorides on the columns used must be close to that for one of the 1,2-dichlorides so that the presence of the rearrangement would remain undetected. Since both the 1,2-diequatorial dichloride and the 1,3-dichlorides have dipole moments on the order of the group moment for a C-Cl bond, whereas the 1,2-diaxial dichloride has only a small dipole moment, the retention times for the 1,3-dichlorides might be comparable to that for the 1,2-diequatorial dichloride.

There is some suggestion in the infrared spectrum of the dichloride mixture that 1,3-dichlorides are present. The weak absorption band occurring at 709 cm^{-1} did not change in intensity on distillation of the mixture of dichlorides. Bennett and Niemann observed a similar absorption band in one product fraction of the reaction of hydrochloric acid with cis-1,4-epoxycyclohexane (93). This product fraction was thought to contain primarily 1,3-dichlorocyclohexanes.

The infrared result mentioned above is only suggestive, and further experimental work needs to be done. For example, if a residual dichloride fraction remained after a thorough attempt to dechlorinate the diequatorial dichloride product with zinc in ethanol or acetamide, this would constitute evidence for the presence of dichlorides other than the 1,2-dichloride. The 1,3-dichlorocyclohexanes have not been well characterized and studied as yet, and it would be useful to have information on infrared spectra, reactivity towards zinc, etc.

4. EXPERIMENTAL

4-t-Butylcyclohexyl Acetate

Vapor phase chromatography of a dilute solution of Matheson reagent grade 4-t-butylcyclohexanol on a Perkin-Elmer Carbowax 1500 column at 143° indicated the alcohol to be a mixture of 18% *cis*-4-*t*-butylcyclohexanol and 82% *trans*-4-*t*-butylcyclohexanol. The crystalline mixture of 4-*t*-butylcyclohexanols (50 g., 0.32 mole), 3 g. of anhydrous sodium acetate, and 125 ml. of acetic anhydride were refluxed for 4 hours. The reaction mixture cooled to room temperature was poured with stirring into 1 l. of cold water. After standing one hour with occasional stirring to insure complete hydrolysis of the acetic anhydride, the mixture was extracted with three 100 ml. portions of pentane. The combined pentane extracts were washed twice with 200 ml. of water followed by single washings with 100 ml. of 2% sodium hydroxide solution and 100 ml. of water and were dried over anhydrous magnesium sulfate. The pentane was distilled from the filtered solution on a steam bath. The liquid residue was distilled under vacuum through a 22 cm. long, 1.5 cm. inside diameter pyrex column packed with stainless steel gauze cylinders (3 x 3 mm, 2700 mesh/cm^2 supplied by Eggmann and Company, Basel 3, Switzerland). The product fraction was collected in a receiver cooled in a dry-ice-acetone mixture, b.p. 125-128°, 18 mm. Hg., 52.3 g. 82%. A second preparation on twice the scale yielded 84%. Vapor phase chromatography of an initial portion of the collected fraction indicated the presence of about 25% of *cis*-4-*t*-butylcyclohexyl acetate.

4-*t*-Butylcyclohexene

a. Pyrolysis of 4-*t*-Butylcyclohexyl Acetate.--4-*t*-Butylcyclohexyl acetate (15.4 g., 0.078 mole) was added dropwise at a rate of 3 to 6 drops per minute and under a slow stream of helium onto the top of a 2.5 cm. diameter vertical quartz column packed over a length of 23 cm. with pyrex helices and heated to 460° in a combustion furnace. The pyrolysis product was collected at the lower end of the column in a flask cooled in a dry-ice-acetone mixture. The pyrolysis was considered complete one hour after the ester addition to the top of the column was completed. The column was cooled to room temperature and was washed with 90 ml. of pentane which was added to the product mixture. The pentane solution was washed with 90 ml. of water, 100 ml. of 5% sodium hydroxide solution, and finally with 100 ml. of water. The pentane solution was dried over calcium chloride, filtered, and the pentane was distilled through a 45 cm. long column, 1.5 inside diameter, packed with pyrex Raschig rings. The remaining liquid residue was vacuum distilled through a 20 cm. long, vacuum jacketed Podbielniak column, and the fractions were collected in receivers, cooled in a dry-ice-acetone mixture, 6.13 g., yield 62%; b.p. 78°-83°, 42 mm. Hg.; 55°- 59°, 12 mm. Hg. That the product was a single substance was indicated by vapor phase chromatography on silicone rubber at 150° and

Carbowax 1540 at 116°. The infrared spectrum taken neat between salt plates had maxima at 1660(w), 1480(m), 1438(w), 1392(w), 1364(s), 1245(w), 1230(w), 910(w), 700(s) cm^{-1}. The yields on three similar preparations were 79%, 68%, and 48%. The pyrolysis column had to be repacked with new, clean helices between runs since otherwise tars and polymers contaminated the product. Pyrolysis was very slow and incomplete below a column temperature of 400°. The olefin was stored in a refrigerator under an oxygen-free nitrogen atmosphere with a few crystals of hydroquinone added to suppress hydroperoxide formation.

b. Dehydration of 4-*t*-Butylcyclohexanol.--Matheson reagent grade 4-*t*-butylcyclohexanol (22.21 g., 0.142 mole) and 10 ml. of 85% phosphoric acid (Merck reagent) were heated to 168° in a silicone oil bath under a helium atmosphere. The product was distilled as it formed through a Podbielniak column (tantalum wire coil). The temperature of the distilling vapor remained at 93° ± 1° over a period of 4 hours during which time the temperature of the oil bath was gradually increased to 215°. The organic layer of the product was separated from the aqueous layer, dried over calcium chloride, and vacuum distilled through the Podbielniak column. A single fraction, bp. 73-77°, 32 mm. Hg., was collected, 9.70 g., yield 50%. The infrared spectrum taken neat between salt plates had maxima at 3040(m), 2970(s), 2900(s), 2880(s), 2850(m), 1658(w), 1480(m), 1465(m), 1438(m), 1392(m), 1364(s), 1246(w), 1232(w), 920(w), 910(w), 802(w), 720(w), 702(m) cm^{-1}. Vapor phase chromatography on Carbowax 1540 at 75° gave three peaks of similar retention times present in relative amounts 7:3:9 in order of increasing retention time. The slowest moving peak has a retention time identical to that of 4-t-butylcyclohexene. All three peaks were identified with similar peaks obtained when pure 4-t-butylcyclohexene was treated with acetic acid containing a catalytic amount of perchloric acid. The nuclear magnetic resonance spectra showed two kinds of t-butyl groups in relative amounts of 63% and 37%.

Bromination of 4-t-Butylcyclohexene in Benzene.--A solution of 4-t-butylcyclohexene (4.581 g., 0.0331 mole) dissolved in 25 ml. of dry benzene (distilled from calcium hydride) was stirred and cooled to 3° in a 100 ml. red, low actinic pyrex flask covered with aluminum foil and immersed in an ice bath. A solution of bromine (5.47 g., 0.0342 mole) in 14 ml. of dry benzene was added dropwise with stirring at such a rate that the temperature remained below 6°. At the end of an hour the solvent was distilled into a dry-ice cooled trap under vacuum at a temperature slightly below 25°. Titration of the distillate with .01 N sodium hydroxide required less than 30 ml. The composition of the residue did not change measurably with time. The infrared spectra in the 600 cm^{-1} to 800 cm^{-1} region had maxima at 645(w), 678(s), and 773(w) cm^{-1}. The nuclear magnetic resonance spectrum in the -hydrogen region indicated the presence of 9% of 1(e), 2(e)-dibromo-4(e)-*t*-butylcyclohexane and about 91% of 1(a), 2(a)-dibromo-4(e)-*t*-butylcyclohexane.

Chlorination of Pentane in the Presence of Anthracene.--Matheson reagent anthracene (1.45 g., 0.006 mole), m.p. 213-214°, was dissolved in 140 ml. of benzene and 70 ml. of pentane in a low actinic, red pyrex flask covered with aluminum foil. The solution was stirred and cooled to about 23° and dry chlorine gas was bubbled into it. At the end of 1/2 hour the anthracene had been chlorinated since chlorinated anthracene derivatives were isolated, but no chloropentanes were formed as indicated by vapor phase chromatography.

Chlorination of 4-*t*-Butylcyclohexene

a. *In Pentane.*--A solution of 4-*t*-butylcyclohexene (3.40 g., 0.025 mole) and 0.022 g. of 2,6-di-*t*-butyl-*p*-cresol in 50 ml. of distilled pentane was stirred in a low actinic, red pyrex flask covered with aluminum foil and cooled in an ice bath. Chlorine gas from a cylinder was dried by bubbling through concentrated sulfuric acid and thence into the reaction flask at a rate such that the temperature remained below 7°. At intervals of a few minutes aliquots of the reaction mixture were removed and chromatographed on a silicone rubber column at 175°. The chromatograph results are listed in Table IV. The aliquots when initially removed were yellow; the color disappeared in a few seconds. Near the end of the reaction the presence of hydrogen chloride was noticed, and increasing amounts of chloropentanes were found in the later aliquots. The low retention time chloropentanes were identified with the products of light induced chlorination of pentane. The composition of the aliquots did not change measurably over a period of 24 hours. The average composition of the aliquots was 26.3% of diequatorial isomer with a standard deviation of 1.9%.

After sitting four hours at room temperature, the reaction mixture was poured into 75 ml. of water, the reaction flask rinsed out with 25 ml. of pentane, and the layers separated. The organic layer was washed with 75 ml. of water, 75 ml. of 5% sodium hydroxide, and finally with 75 ml. of water and was dried over calcium chloride. The pentane was distilled from the filtered solution, and the liquid residue remaining was vacuum distilled through a Podbielniak column. The dichloride product fraction boiled 100-104°, 6 mm. Hg., 2.258 g., 44%. Vapor phase chromatography indicated approximately 11% of the long retention time isomer and 89% of the other dichloride isomer in the dichloride mixture.

TABLE IV

Chromatograph of Aliquots of Chlorination in Pentane

Time,* minutes	% Long retention time isomer‡	Comments
10	----	Chlorine flow small, no reaction.
30	----	No reaction.
45	----	Still no apparent reaction, flow increased.
65	30.3, 29.3, 28.0	Aliquots are initially yellow.
75	25.7, 27.3, 26.2	
85	24.7, 25.3, 26.7	
95	25.6, 25.9, 21.8	
105	26.6, 28.1, 28,0	
145	23.9, 24.7, 26.6	
170	25.8, 25.9, 25.6	Reaction nearly complete judging by olefin peak.

*Zero time was taken at the initiation of chlorine flow.

‡For each aliquot three measurements of peak area were performed.

Anal. calculated for $C_{10}H_{18}Cl_2$: C, 57.42%; H, 8.67%; Cl, 33.90%. Found: C, 57.27%; H, 8.57%; Cl, 33.69%.

After a week the composition of the dichloride mixture was found to be 16.5% ± 1.1% (standard deviation) of the long retention time isomer. The infrared spectrum taken of the pure liquid in a 0.025 cm. cell had maxima at 2900(s), 2830(s), 1475(s), 1448(m), 1430(s), 1392(w), 1362(s), 1342(w), 1322(w), 1307(w), 1278(w), 1238(m), 1212(s), 1169(w), 1147(w), 1035(w), 1020(m), 981(m), 932(w), 906(w), 883(m), 856(w), 819(s), 793(w), 776(m), 740(w), 708(w), 683(m) cm^{-1}.

A solution of the above mixture of 4-*t*-butylcyclohexyl-1,2-dichlorides (0.893g.) and 2,6-di-*t*-butyl-*p*-cresol (0.065 g.) in 10 ml. of distilled pentane in a flask protected from light was cooled to below 2° in an ice bath, and dry chlorine gas was passed through the stirred solution. Aliquots were removed at intervals and chromatographed on silicone rubber. The results are given in Table V. The composition remained at 15.6 ± .6% of the long retention time isomer for all aliquots.

b. *In Benzene*.--Dry chlorine (0.84 g., 0.012 mole) dissolved in 11 ml. of dry benzene (distilled from calcium hydride) was added dropwise to a stirred solution of anthracene (0.226 g., 0.001 mole) and 4-*t*-butylcyclohexene (1.687 g., 0.0122 mole) in 45 ml. of dry benzene cooled to 7°. The reaction was protected from light as above. Aliquots of the

TABLE V

Chromatograph of Aliquots of Dichlorides

Time,* minutes	% Long retention time isomer
18	15.2
42	14.7
56	15.8
79	16.5, 16.6
92	14.9
109	15.6
132	15.7
158	16.0

*Zero time was taken at the moment of chlorine flow initiation.

reaction mixture were removed at intervals and chromatographed. Little chlorination of the olefin occurred so that additional chlorine was added until the chlorination of the olefin was essentially complete. The solvent, excess chlorine, and hydrogen chloride formed were removed under reduced pressure and collected in a dry ice trap. Water was added to the trapped mixture, and the mixture was titrated with 0.00929 N sodium hydroxide to a phenolphthalein end point. A total of 14.50 ml. of base was required indicating the presence of 1.34×10^{-4} moles of acid. Vapor phase chromatography of the chlorinated residue indicated the presence of 28.4% ± 1.1% of the long retention time isomer relative to the total dichloride formed.

c. *In Chlorobenzene*.--A solution of 4-*t*-butylcyclohexene (4.20 g., 0.0305 mole) dissolved in enough chlorobenzene to make a total volume of 50.0 ml. at 26° was cooled to below 5° in a low actinic, red pyrex flask covered with aluminum foil and cooled in an ice bath. While stirring, chlorine gas was bubbled through the solution at a rate such that the temperature remained below 5°. Aliquots of the reaction mixture were removed at intervals (Table VI). The average composition of the last three aliquots was found to be 41.1% ± 1.6% of the long retention time isomer. All aliquots were colorless although a dilute solution of chlorine

TABLE VI

Chromatograph of Aliquots of Chlorination in Chlorobenzene

Time,* minutes	% Long retention time isomer
5	36, 30 (may be large error because peaks are small)
20	42.6
28	39.5
40	41.2

*Zero time was taken at the moment of chlorine flow initiation.

in chlorobenzene is yellow and remains yellow for several hours. After 40 minutes from the time of chlorine flow initiation the presence of a slight amount of hydrogen chloride was detected. A 5.00 ml. aliquot was removed, delivered to 25 ml. of water, and titrated with 0.00929 N sodium hydroxide to a phenolphthalein end point. The volume of base required was 3.60 ml. corresponding to a total of 3.34×10^{-4} moles of hydrogen chloride in a reaction mixture of 50 ml.

The reaction mixture was neutralized with 0.01 N sodium hydroxide, and the chlorobenzene layer was separated, washed with 50 ml. of water, and dried over calcium chloride. The filtered solution was distilled under vacuum through a Podbielniak column. The first fraction, b.p. 79-82°, 141 mm. Hg., was primarily chlorobenzene with some unreacted olefin. The second and third fractions were mostly unreacted olefin. A fourth fraction contained the dichlorides, 1.153 g., 18%, b.p. 112-115°, 13 mm. Hg. This fraction consisted of 32% of the long retention time isomer.

d. <u>In Acetic Acid</u>.--Chlorine gas was bubbled into a stirred solution of 4-*t*-butylcyclohexene (1.345 g., 0.01 mole) in 20 ml. of glacial acetic acid (Baker's reagent) cooled such that the temperature remained at 15-17°. Ten to fifteen minutes were required before the solution turned yellow and the temperature started to drop. The chlorine addition was stopped. After 4 hours at room temperature chlorine was still present. The mixture was poured into 40 ml. of water and extracted with 15 ml. of pentane. The pentane layer was separated, washed with 15 ml. of water, and with 15 ml. of 5% sodium hydroxide which removed the remaining chlorine. The pentane solution was dried over calcium chloride, filtered, and evaporated to approximately 5 ml. under a stream of helium. Vapor phase chromatography of the residue on a Carbowax 1540 column at 200° indicates between 70% and 75% of the mixture to be composed of the long retention time isomer. A more accurate quantitative determination was not possible due to overlapping of the peak with that of an unknown substance.

A mixture of dichlorides containing about 32% of the long retention time isomer (0.30 g.) was dissolved in 2.5 ml. of glacial acetic acid (Baker's reagent). At intervals of several hours 30 μl. aliquots were removed and chromatographed on a Carbowax 1540 column at 200°. The mixture was allowed to stand at room temperature for four days. The mixture was poured into a few ml. of water and extracted with pentane. The combined pentane extracts were washed twice with 5 ml. portions of water, once with 5% sodium hydroxide, and once more with water. The pentane solution was dried over magnesium sulfate, filtered, and evaporated to a few milliliters under a stream of helium. A sample was chromatographed as above.

Although the presence of acetic acid hindered the quantitative analysis of the chromatographic curves no apparent change in composition occurred in the first few hours. However, in the dichloride mixture obtained upon removal of acetic acid was found 41% of the long retention time isomer.

4-t-Butylcyclohexanone.--To potassium dichromate (33 g., 0.11 mole) dissolved with stirring in 200 ml. of water at 55° C was added 20 ml. of conc. sulfuric acid followed by 4-t-butylcyclohexanol (Eastman reag., 52.08 g., 0.33 mole). The reaction mixture was stirred and maintained at 55-60° by heating on a water bath for 1/2 hour, then cooled to room temperature and allowed to stand for several hours. The reaction mixture was extracted with two 100 ml. portions of pentane, and the pentane extract washed successively with two 100 ml. portions of water, 100 ml. of 5% sodium hydroxide, and 100 ml. of water. The extract was dried over anhydrous magnesium sulfate overnight, filtered and the pentane removed by distillation under reduced pressure. A short path vacuum distillation of the product gave 39.48 g. (76%) of 4-t-butylcyclohexanone, b.p. 102.5-108° (14 mm.), the infrared spectrum of this material showed no hydroxyl band and a strong ketone carbonyl band.

1,1-Dichloro-4-*t*-butylcyclohexane and 1-Chloro-4-*t*-butylcyclohexene.--To phosphorus pentachloride (analytical reagent, 26.0 g., 0.125 mole) and 100 ml. of methylene chloride contained in a 200-ml. 3-necked round-bottom flask fitted with a mechanical stirrer, thermometer, and pressure-equalized dropping funnel and cooled to -10° by an ice-salt bath was added dropwise with stirring over a period of 1 hour a solution of 4-*t*-butylcyclohexanone (15.42 g., 0.100 mole) in 20 ml. of methylene chloride; during the addition the temperature rose to -3°. The mixture was stirred for an additional 2 1/2 hours at a temperature of -3 to +7° and then for an hour up to room temperature. The mixture was poured onto 200 g. of ice, the layers separated, and the organic layer washed with two 100 ml. portions of water and then stirred with 100 ml. of 5% sodium hydroxide mixed with 100 g. of ice. The organic portion was separated, dried over calcium chloride, and the calcium chloride removed by filtration. A vapor phase chromatograph of the methylene chloride solution indicated that the product consisted of 82% 1-chloro-4-*t*-butylcyclohexene and 18% of 1,1-dichloro-4-*t*-butylcyclohexane, if it is assumed that the component with the longest column retention time is the dichloride. The methylene chloride was removed by distillation through a Vigreaux column on a steam bath.

1-Chloro-4-*t*-butylcyclohexene.--To potassium hydroxide pellets (40 g.) mixed with 50 ml. of 95% ethanol maintained at reflux was added cautiously a solution of the product from the previous step in 25 ml. of 95% ethanol, followed by a 10 ml. ethanol wash. The mixture was maintained at reflux for 3 hours, poured onto 500 ml. of ice and water to give a milky suspension. The mixture was extracted with three 50 ml. portions of methylene chloride, the organic extract washed with water and dried over calcium chloride. The solvent was distilled through a 45 cm. column packed with Raschig glass rings and the residual product was vacuum distilled through a Podbielniak column to give two forerun fractions (1.16 g., b.p. 25-74°, 6 mm. Hg. and 1.32 g., b.p. 74-79°, 6 mm. Hg., respectively) and a product fraction, 2.26 g., b.p. 100-104°, 6 mm. Hg. The retention time of the product on a Carbowax column differed greatly from the retention times of either product of the chlorination of 4-*t*-butylcyclohexene. The infrared spectrum of the product in a 0.025 cm. cell had maxima at 2900(s), 1659(m), 1468(s), 1433(m), 1390(m), 1362(s), 1343(m), 1295(w), 1257(w), 1240(w), 1169(w), 1148(w), 1048(s), 1022(s), 980(s), 963(m), 940(w), 907(m), 827(m), 806(m), 717(s) cm^{-1}.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.54; H, 9.92; Cl, 20.53. Found: C, 69.44; H, 10.34; Cl, 20.21.

Chlorination of Cyclohexene

a. Cyclohexene.--Cyclohexene (Eastman reagent, 100 ml.) was shaken with a solution of 10 g. of sodium hydrosulfite in 100 ml. of distilled water. The olefin layer was separated and dried over calcium chloride under an oxygen-free nitrogen atmosphere in a low actinic, red pyrex flask. The filtered cyclohexene was distilled in an oxygen-free nitrogen atmosphere, b.p. 80.5°, 745.2 mm. Hg. The first 25 ml. was discarded.

b. Chlorination in Carbon Tetrachloride.--To a stirred solution of chlorine (3.2 g., 0.045 mole) in 40 ml. of carbon tetrachloride (Baker's reagent) cooled to -8° in an ice-salt bath and protected from light was added dropwise a solution of cyclohexene (3.69 g., 0.045 mole) in 20 ml. of carbon tetrachloride at such a rate that the temperature remained below 4°. A vapor phase chromatograph of a sample of the carbon tetrachloride solution on a Carbowax 1500 column at 145° and 121° indicated the presence of a single product.

c. Chlorination in Carbon Tetrachloride under Ultraviolet Radiation.--Dry chlorine was passed through a solution of cyclohexene (3.794 g.) in 30 ml. of carbon tetrachloride while the solution was irradiated with light from a General Electric Purple X bulb. Vapor phase chromatography indicated the presence of two substances. The major component had the longest retention time, was identical to the product of the chlorination in absence of light, and was present in about 91%.

Stability of 4-t-Butylcyclohexene in Acetic Acid.-- A solution of 4-t-butylcyclohexene (1.01 g.) in 5 ml. of glacial acetic acid containing 3 drops of 60% perchloric was heated on a steam bath for one hour. The reaction was cooled briefly and poured into 10 ml. of water and 10 ml. of pentane. The pentane layer was separated, washed with 10 ml. of water, 10 ml. of 5% sodium hydroxide, and dried over potassium carbonate. A sample chromatographed on a Carbowax 1540 column at 158° indicated that only about 75% of the olefin remained and that this olefin was isomerized to the extent of about 30% into the other positional isomers. Four products, two of which were identified as cis-4-t-butylcyclohexyl acetate and trans-4-t-butylcyclohexyl acetate and came off the chromatographic column second and last, respectively, were present in relative amounts of 39%, 36%, 15%, and 10% in order of increasing retention times.

In another experiment the reaction mixture was allowed to stand at room temperature for about three hours after heating on a steam bath for one hour. The composition of the acetates was then, in the order of increasing retention time, 32%, 23%, 25%, and 20%. Extensive isomerization of olefin had occurred.

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III.

LITHIUM ALUMINUM HYDRIDE REDUCTION OF CIS-2,6-DIMETHYLCYCLOHEXANONE

1. INTRODUCTION

The work reported here comprises a brief study of a steric effect in reactions of 2,6-disubstituted cyclohexyl derivatives which may be thought of as corresponding to the "ortho" effects observed in aromatic systems (1).

1.1 Lithium Aluminum Hydride Reduction of Ketones

Reduction of ketones with lithium aluminum hydride usually gives as the predominant product the most stable alcohol (2, 3, 4, 5). However, sterically hindered ketones such as camphor and 2-cholestanone give alcohols resulting from the addition of hydrogen to the least hindered side of the ketone (4, 5, 6, 7). Such results have led to the formulation of the concepts of "product development control" and "steric approach control," (3, 4). The probable mechanism (8) is depicted in figure 1. Coordination of the carbonyl group with the hydride complex is followed by the attack of the hydride donating species at the carbonyl carbon. The latter step is rate-determining as well as product-determining. The complexation with the carbonyl oxygen may effectively increase its bulk to a considerable extent (8) which increases the tendency of this group to occupy an equatorial position. It is easy to see when conformational preferences are taken into account that this effect would lead to the predominant formation of <u>trans</u>-alcohols from 4-substituted cyclohexanones, <u>cis</u>-alcohols

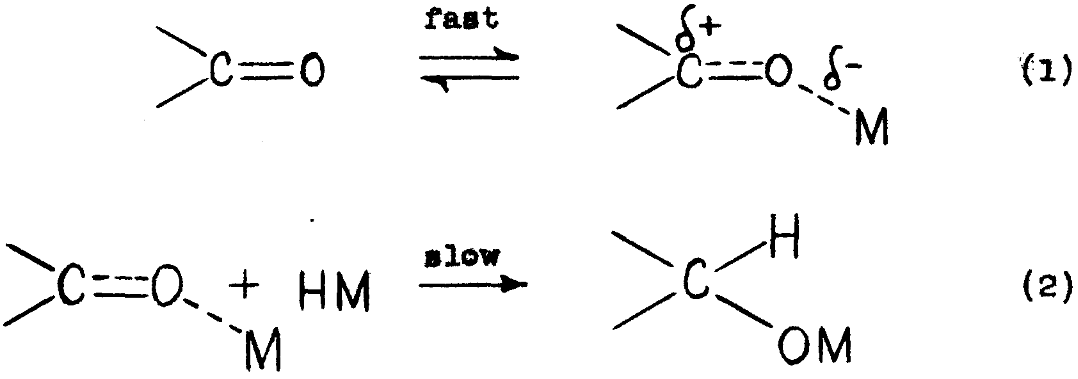


Figure 1.

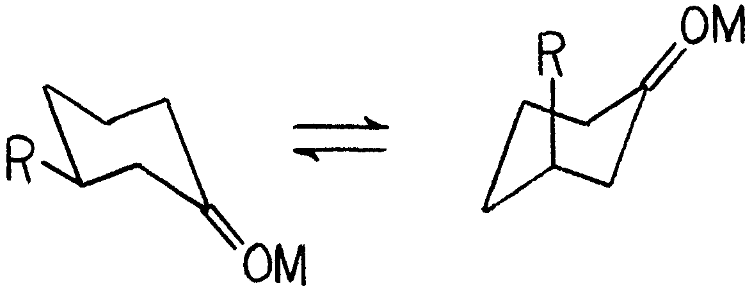


Figure 2.

from 3-substituted cyclohexanols, and trans-alcohols from 2-substituted cyclohexanols. Thus, "product development control" or the most stable product is predicted by these considerations.

Table I gives the percentages of trans-alcohol from the reduction of some 4-alkyl substituted cyclohexanones and 4-phenylcyclohexanone. It is apparent that these results are in agreement with the above prediction.

TABLE I

Lithium Aluminum Hydride Reduction of 4-Substituted Cyclohexanones

Ketone	% Trans.
4-t-butyl	91-93 (9,10), 88-90 (11)
4-methyl	81 (4), 75 (12), 79-81 (9,11), 84 (21)
4-cyclohexyl	43 (12)
4-phenyl	90-91 (11)

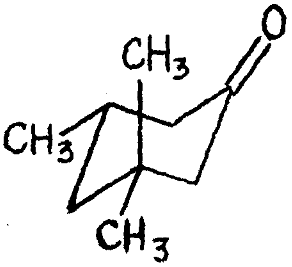
The reduction of 4-methylcyclohexanone gives less trans-alcohol than 4-t-butylcyclohexanone because the methyl group is not restricted to an equatorial position; the free energy difference between an axial and equatorial methyl is 1.6 to 1.8 kcal/mole (13, 14). In view of the other results, the case of 4-cyclohexylcyclohexanone should be confirmed. One would expect the 4-cyclohexyl group to be almost as effective as the 4-isopropyl group in holding configuration.

Table II lists the percentages of cis-alcohols formed by reduction of some 3-substituted cyclohexanones. Here the results are complicated by the occurrence of two steric effects, steric hindrance involving complex formation and, since the alkyl group when in the axial position is on the side of axial hydride donor approach, steric hindrance to hydride donor approach in one conformation (fig. 2). This latter steric effect should lead to an increase of the thermodynamically stable product over that from the corresponding 4-substituted cyclohexanone. The results for 4-methyl- and 3-methylcyclohexanones bear this out. The case of 3,3,5-trimethylcyclohexanone is interesting since it represents a limiting example of the effect of an axial 3-methyl group. The conformation I (fig. 3) is held since the 1,3-diaxial interaction of two methyl groups is expected to be high. A comparison of the result for 3,3,5-dimethylcyclohexanone with 4,t-butylcyclohexanone indicates that there is a

TABLE II

Lithium Aluminum Hydride Reduction of
3-Substituted Cyclohexanones

Ketone	% cis
3-methyl	92 (4), 89 (12), 85 (9), 87 (21)
3,3,5-trimethyl	50 (12)



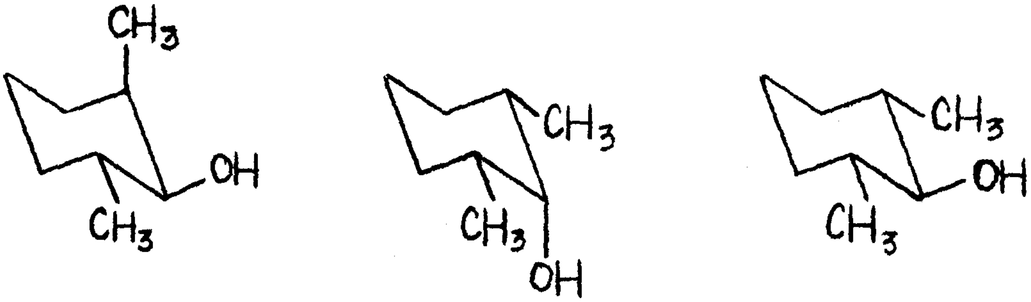
I

Figure 3.

II

III

Figure 4.



IVa

IVb

IVc

Figure 5.

large steric hindrance to hydride donor approach due to a 3-axial methyl.

Table III lists the percentages of trans-2-substituted alcohols formed by the reduction of some 2-substituted cyclohexanones and 2-substituted cyclopentanones. One is struck by the fact that the proportion of thermodynamically stable product (trans-alcohol) decreases as the bulk of the 2-substituent increases. It appears that a new steric effect is beginning to dominate which is somehow connected with the bulk of the substituents around the carbonyl group. This suggests the possibility that two methyl groups flanking the carbonyl would have an even more exaggerated effect.

TABLE III

Lithium Aluminum Hydride Reductions of Some 2-Alkyl Substituted Cyclohexanones and Cyclopentanones

Ketone	% trans
2-methylcyclohexanone	82 (3), 64 (4,15), 60 (12), 70 (21)
methone	71 (4)
2-t-butylcyclohexanone	51 (16)
2-cyclohexylcyclohexanone	mostly cis (23)
2-methylcyclopentanone	75 (2)
2-isopropylcyclopentanone	43 (17), mostly cis (23)
2-ethylcyclopentanone	mostly cis (23)

1.2 Steric Hindrance in the Saponification of the 2,6-Dimethylcyclohexyl Acid Phthalates

The saponification rates of esters of 2,6-dialkylcyclohexanols indicate the presence of steric hindrance in these systems.

Table IV gives values of rate constants (in l. mole^{-1} sec^{-1}) for saponification of 4-*t*-butylcyclohexyl acid phthalate and the 2,6-dimethylcyclohexyl acid phthalates. The 2,6-dimethylcyclohexyl acid phthalates exhibit markedly reduced reactivity when compared with *cis*-4-*t*-butylcyclohexyl acid phthalate. The *cis*-4-*t*-butyl cyclohexyl esters generally saponify slower than other cyclohexyl derivatives except in such cases as these where steric hindrance at the reaction site completely dominates the reaction. Indeed, because of this it is not possible to dissect the rate constants in the conventional manner (14) into the mole fractions in each conformation, since the observed rate constant must be intermediate between the extreme cases of *cis*- and *trans*-4-*t*-butylcyclohexyl esters for this procedure to be applied.

TABLE IV

Saponification of Acid Phthalates

Acid phthalate	Temp., °C	Solvent	$k_2 \times 10^5$
trans-4-*t*-butylcyclohexyl	69°	H_2O	43.3 (14)
cis-4-*t*-butylcyclohexyl	69°	H_2O	54.5 (14)
$2\alpha,6\beta$-dimethylcyclohexyl-1α	70°	10% EtOH-H_2O	21.3 (18)
$2\alpha,6\beta$-dimethylcyclohexyl-1β	70°	10% EtOH-H_2O	7.2 (18)
$2\alpha,6\alpha$-dimethylcyclohexyl-1α	70°	10% EtOH-H_2O	1.3 (18)

The rate difference between *cis*- and *trans*-4-*t*-butylcyclohexyl acid phthalates is much larger than the rate difference between the "all *cis*" and "all equatorial" isomers which may be assumed to have preponderantly a single conformation each, II and III (fig. 4), respectively. Although the "all *cis*" isomer II is slowest, the difference is but a factor of 5.5 in rate. This may be explained if the steric crowding of the methyl groups is of comparable or greater effect than the steric difference between axial and equatorial groups in slowing the saponification rate. Similar results have been observed in the 2,6-dipropylcyclohexyl and 2,6-dibenzylcyclohexyl systems (19, 22).

The extent to which such steric effects are to be found in the less sterically hindered 2-alkylcyclohexyl systems is difficult to assess, but one must hold reservations concerning conformational analyses which neglect this possibility.

1.3 Steric Acceleration of Solvolyses

Another example of steric effects in 2-substituted cyclohexyl derivatives is provided by the solvolysis of 2-*t*-butylcyclohexyl tosylates (20). It was found that the *cis*-2-*t*-butylcyclohexyl tosylate was acetolysed 90 times faster than *cis*-4-*t*-butylcyclohexyl tosylate, and the *trans*-2-isomer was 145 times faster than the *trans*-4-isomer. These rate differences were attributed to steric acceleration of the rate, i.e. the steric crowding of the *t*-butyl group and tosylate group raised the energy of the ground states.

2. RESULTS

Hydrogenation of 2,6-xylenol in ethanol over platinum gave a mixture of the three isomers of 2,6-dimethylcyclohexanol, IV, with vapor phase chromatograph retention times of 8.2, 10.6, and 13.4 minutes on a diisodecylphthalate column at 140° and present in 5%, 59%, and 36%, respectively. Hydrogenation in acetic acid over platinum gave only the isomers of retention times 10.6 and 13.4 minutes in about 90% and 10%, respectively. Since the isomer with the retention time of 10.6 minutes predominates in both hydrogenations it is probably the "all cis" isomer, IVb (fig. 5). Oxidation of a mixture of these two isomers (retention times 10.6 and 13.4 minutes) gave a single ketone. Furthermore, treatment of a mixture of the two isomers with sodium metal and a trace of ketone at 210° converts the isomer of retention time 10.6 minutes into the isomer of longest retention time, the most thermodynamically stable isomer, IVc. The ketone must be cis-2,6-dimethylcyclohexanone, V (fig. 6). Lithium aluminum hydride reduction of V gave 14% of IVc and 86% of IVb.

V

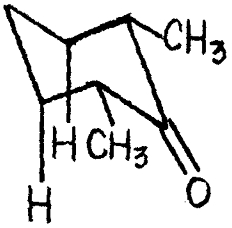


Figure 6.

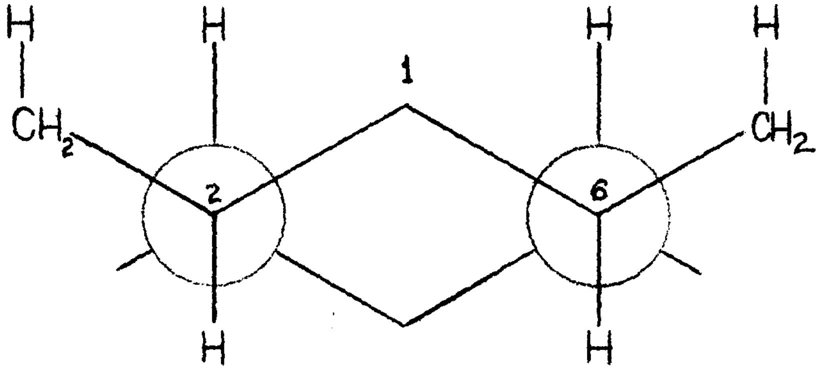


Figure 7.

3. DISCUSSION

3.1 Ring Deformation and Steric Hindrance

The 1(e), 2(e) interactions between substituents on the cyclohexyl ring may be relieved by a ring deformation in which the interfering groups are allowed to bend away from each other and in so doing cause distortion of the normal chair configuration of the ring (24). The 2,6-dialkylcyclohexyl system is complicated by this effect as well as steric hindrance to reactions occurring at the 1-position.

The steric hindrance in the 2,6-dialkylcyclohexyl system has at least two sources. Some of the steric hindrance comes from the flanking of the reaction center (the 1-position) by two alkyl groups. In addition, an effective source of hindrance stems from the combined buttressing of the angular methyls and the 3,5-axial hydrogens (fig. 7). For the staggered conformation of the angular methyls, the reaction center is in effect surrounded by four 1,3-diaxial hydrogens on a single side of the ring.

3.2 Lithium Aluminum Hydride Reduction of *cis*-2,6-Dimethylcyclohexanone

The result that lithium aluminum hydride reduction of *cis*-2,6-dimethylcyclohexanone gives but 14% of the most stable isomer is very striking in comparison with the other results as reported in Table III since this result constitutes the most extreme so far discovered. The result also substantiates the hypothesis that steric effects are important in lithium aluminum hydride reductions. Two equatorial groups adjacent to a reaction site thus cause severe steric hindrance.

3.3 Possible Isomerization of Alcohols During the Hydride Reduction

The reduction of the trans-2,6-dimethylcyclohexanone would give a single alcohol, namely IVa (page 163) unless isomerization of the alkoxide occurred during the reduction. If the identification of the ketone used in this study as cis-2,6-dimethylcyclohexanone is in error, then the occurrence of isomerization during the ketone reduction could account for the results, and the lithium alkoxides of the alcohols IVa and IVc would be the products formed. This possibility is rendered unlikely since the isomerization of the isomers of IV in sodium ethoxide catalyzed by ketone is very slow even at 210°. Eighteen and one-half hours are required to convert a mixture of alcohols containing 17% of IVc to a mixture containing 50% of IVc, and equilibrium was still not attained. In contrast, the hydride reduction reaction mixture remained at room temperature for a little over one hour.

4. EXPERIMENTAL

Hydrogenation of 2,6-Xylenol

Vacuum distilled 2,6-xylenol (50 g., 0.41 mole) dissolved in 70 ml. of distilled anhydrous acetic acid was hydrogenated over 1.50 g. of platinum dioxide (Baker catalyst, 84.30%) at about three atmospheres of hydrogen at room temperature for 16 1/2 hours. The catalyst was collected on a filter bed of Celite which was then washed with about 100 ml. of acetic acid. To the clear filtrate was added 400 ml. of water and 250 ml. of pentane, the layers were separated, the pentane layer was washed with 300 ml. of water, 250 ml. of 5% sodium hydroxide solution, and again with water, and dried over barium oxide. Acidification of the sodium hydroxide wash gave no unhydrogenated phenol. The drying agent was removed by filtration, and the pentane was distilled on a steam bath leaving a liquid residue, 46 g. Vapor phase chromatography on a diisodecylphthalate column at 140° indicated the presence of small amounts of the 1,3-dimethylcyclohexane isomers. The alcohol mixture was composed of an estimated 90% of an isomer whose retention time was 10.6 minutes and about 10% of an isomer whose retention time was 13.4 minutes. Vacuum distillation of the liquid residue through a 12 mm. diameter 22 cm. long fractionation column packed with 3x3 mm. cylinders of stainless steel wire gauze

(2700 mesh/cm^2) (obtained from Eggmann and Co., Basel 3, Switzerland) yielded the liquid alcohols, b.p. 68-70.5° at 15 mm. Hg. Vapor phase chromatography indicated the presence of two isomers; retention time 10.6 minutes, ~90%; retention time 13 minutes, ~10%.

The 3,5-dinitrobenzoate of the "all cis" isomer was prepared by heating 10 ml. of the alcohol mixture in 80 ml. of pyridine with 20 g. 3,5-dinitrobenzoylchloride on a steam bath for 1/2 hour. The mixture was allowed to stand 1/2 hour at room temperature and then poured into 300 ml. of water. The yellowish solid which precipitated was collected with suction and when air dried yielded 18.0 g. Chromatography of this material dissolved in 100 ml. of methylene chloride and 50 ml. of pentane on 2 kg. of acid-washed alumina packed in pentane gave 6.7 g. of a solid eluted with 7% ether-pentane, m.p. 128-132°. Recrystallization of this solid from ethylacetate gave colorless crystals, 1.9 g., m.p. 133-133.8°. Reported (18), m.p. 133°.

The phenylurethane prepared from the mixture in the usual manner gave colorless crystals on recrystallization from carbon tetrachloride, m.p. 155-157.5°. Reported (25), m.p. 158°.

Another hydrogenation of 2,6-xylenol in 95% ethanol solution over platinum dioxide at 60 atms. at room temperature gave a mixture of all three possible isomers. Vapor phase chromatography on diisodecylphthalate at 140°; 8.2 minutes, 5%; 10.6 minutes, 59%; 13.4 minutes, 36%. Fractional distillation of the mixture through a spinning band column gave middle fractions enriched in the 10.6 minutes retention time isomer whereas a later fraction was nearly free of the 8.2 minute isomer.

cis-2,6-Dimethylcyclohexanone

To a stirred solution of 6 g. of potassium dichromate (0.02 mole) dissolved in a mixture of 30 ml. of water and 3 ml. of concentrated sulfuric acid warmed to 55-60° were added all at once 6 ml. (5.6 g., 0.04 mole) of an alcohol mixture (~90%, 10.6 minute isomer and ~10%, 13.4 minute isomer). The mixture was stirred and maintained between 55-60° for 1/2 hour. The mixture was cooled to room temperature after which 50 ml. of water and 50 ml. of pentane were added, the layers separated, the aqueous layer extracted once with 50 ml. of pentane, and the combined pentane layers washed twice with water, once with 20% sodium carbonate solution, and again with water. The pentane solution was dried over anhydrous magnesium sulfate, filtered, and pentane was distilled from the solution on a steam bath through a 40 cm. long column packed with glass Raschig rings. The brownish liquid residue was vacuum distilled through a Podbielniak column giving a clear colorless liquid, 2.32 g. (39%), b.p. 47-48° at 5 mm. Hg.

Vapor phase chromatography gave a single peak which could not be resolved into two peaks at lower temperatures on different packings. The infrared spectrum was free of hydroxyl absorption but had a strong carbonyl absorption.

Equilibration of the Alcohols

Under an atmosphere of dry O_2-free nitrogen, sodium metal (0.144 g., 0.006 mole) was dissolved in an alcohol mixture containing 83% of the 10.6 minute isomer and 17% of the 13.4 minute isomer (2.340 g., 0.019 mole) by heating to 210° in a 10 ml. pear-shaped flask equipped with a reflux condenser and immersed in a silicone oil bath. After one hour all the sodium had dissolved. A drop of *cis*-2,6-dimethylcyclohexanone was added and the mixture was heated at 210° under a nitrogen atmosphere for a total of 18 1/2 hours. The cooled mixture was carefully poured into 100 ml. of water and 100 ml. of pentane. The layers were separated, the aqueous layer was washed with 50 ml. of pentane, the combined pentane layers were washed with three 50 ml. portions of water, with dilute hydrochloric acid, and finally with water until the washings tested neutral, and the pentane solution was dried over anhydrous magnesium sulfate. The pentane was distilled from the filtered solution giving a liquid residue. Vapor phase chromatography of this residue indicated that about equal quantities of each of the two initially present isomers were present.

Lithium Aluminum Hydride Reduction of *cis*-2,6-Dimethylcyclohexanone

To lithium aluminum hydride (0.5 g., 0.013 mole) contained in a dry 100 ml. flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was added 30 ml. of anhydrous ether. *cis*-2,6-Dimethylcyclohexanone (2.05 g., 0.017 mole) dissolved in 20 ml. of ether was added dropwise with stirring over a period of fifteen minutes. The mixture was stirred for an additional hour and then was hydrolyzed by the cautious dropwise addition of several ml. of water. Dilute hydrochloric acid was added until a solid clump formed below the ether. The ether solution was decanted, and the solids were extracted with three 30 ml. portions of ether. The combined ether solutions were dried over barium oxide, filtered, and the ether distilled leaving a liquid residue. The composition of this liquid as indicated by vapor phase chromatography was 86% of the 10.6 minute isomer and 14% of the 13 minute isomer.

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Proposition I.

The Stereochemistry of 1,2-Hydrogen Migrations in Cyclohexyl Systems.

The following are available examples of 1,2-hydrogen migrations for which stereochemistry has been examined.

Acetolysis of *cis*-4-*t*-butylcyclohexyl *p*-toluenesulfonate at 100° gives 86% olefin and 14% of a mixture of alkyl acetates which has a composition of 40% *trans*-4-*t*-butylcyclohexyl acetate, 30% *cis*-4-*t*-butylcyclohexyl acetate, and 30% *trans*-3-*t*-butylcyclohexyl acetate (1). This latter product must be formed through hydrogen migration since 4-*t*-butylcyclohexene is stable under the reaction conditions, perchloric acid catalyst being necessary in order to affect addition. A mechanism involving two hydrogen bridged intermediates, I and II, explains the formation of *trans*-3-*t*-butylcyclohexyl acetate (Fig. 1).

Acetolysis of *threo*- and *erythro*-3-cyclohexyl-2-butyl *p*-toluenesulfonates (2) at 35° gives 40% to 60% olefin and 10% to 15% acetate which is almost entirely 2-cyclohexyl-2-butyl acetate, i.e. formed through hydrogen migration. Acetate from optically pure *threo*- and *erythro*-tosylates was 35% and 30% optically pure, respectively. The sign of optical rotation was such that these optically active

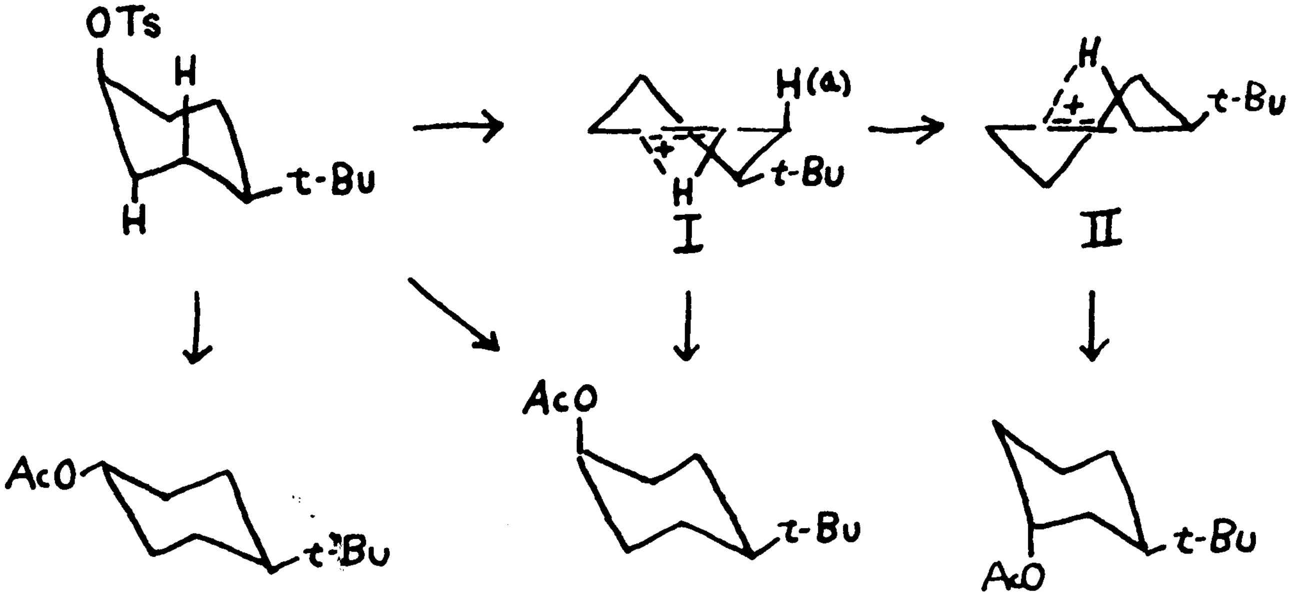

FIGURE 1

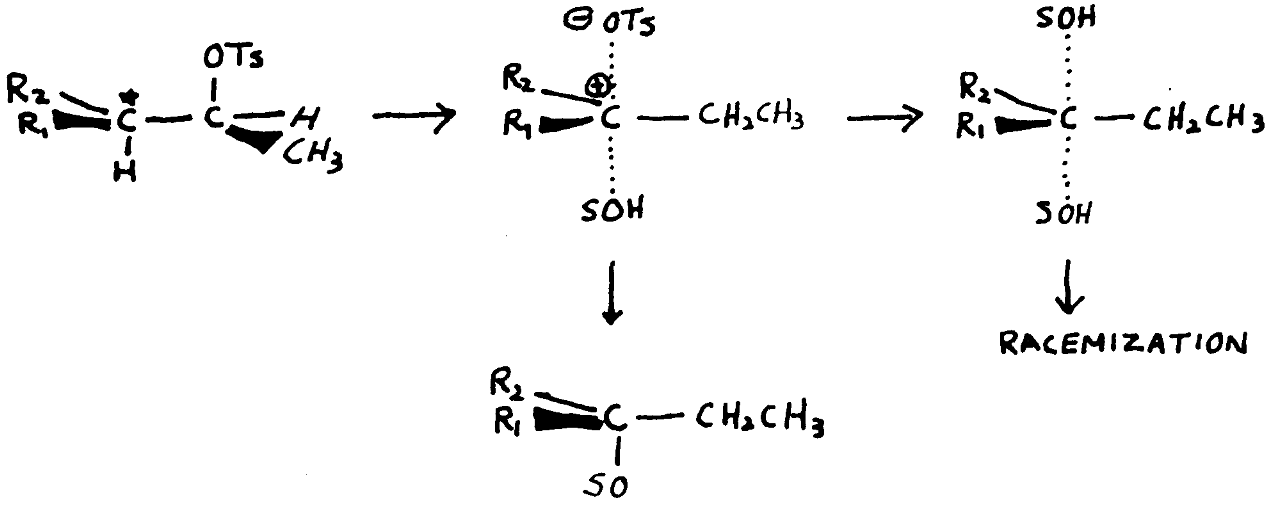

FIGURE 2

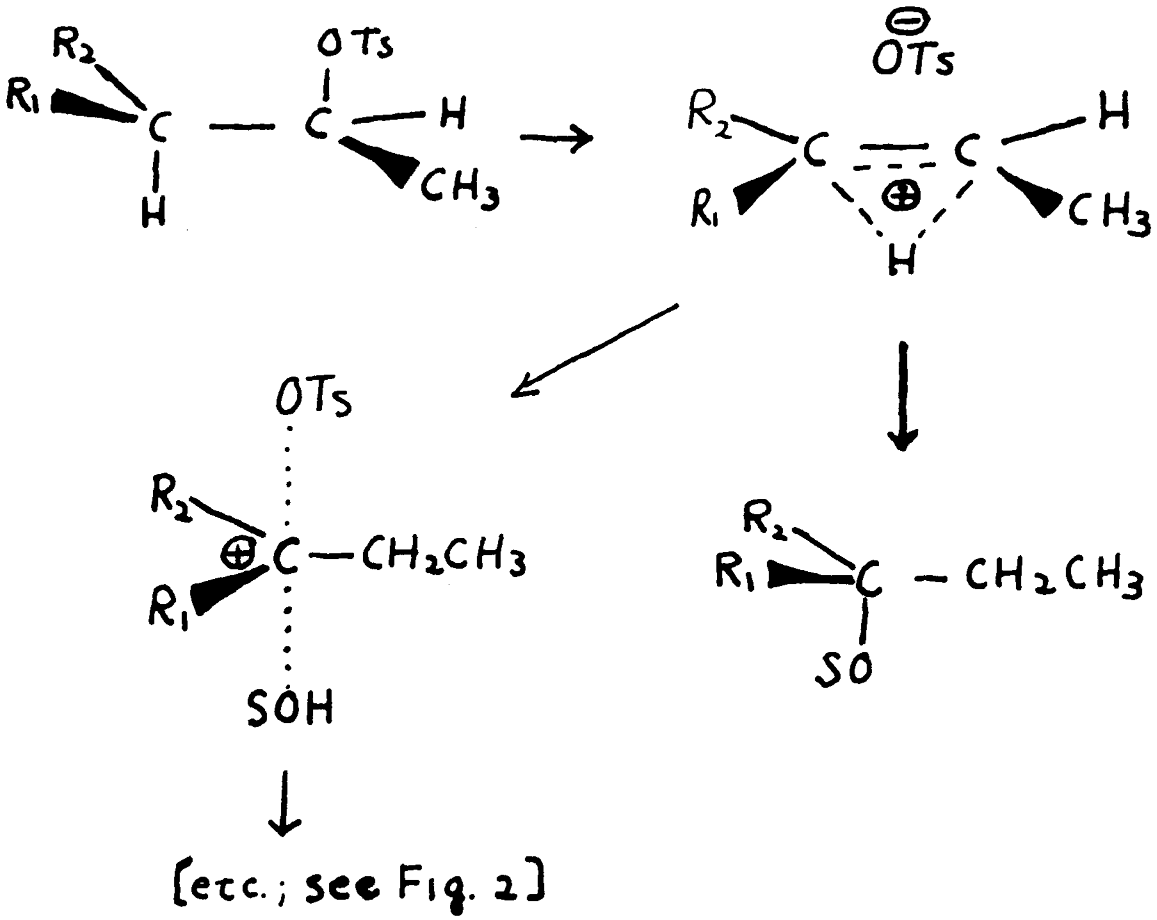

FIGURE 3

acetates must have resulted from nucleophilic attack by solvent on the same side of the migration origin as had been occupied by the migrated hydrogen. The mechanism depicted in Fig. 2 accounts for the observed results.

Among other products, acetolysis of optically active diasteriomers of 3-phenyl-2-butyl _p_-bromobenzenesulfonate at 30° gives racemic 2-acetoxy-2-phenylbutane (3). Under the reaction conditions optically active 2-acetoxy-2-phenylbutane is not sufficiently racemized to account for the whole racemization. A mechanism similar to that in Fig. 2 explains this result.

Although the above mechanisms seem fairly adequate in explaining the results, and additional mechanism involving _cis_ opening of protonium ions has been proposed (2). (Fig. 3) For the 3-cyclohexyl-2-butyl system, this mechanism explains the difference in optical purity of rearranged product for the different diastereoisomeric starting materials. This type of mechanism may also explain the formation of _trans_-3-_t_-butylcyclohexyl acetate from the 4-_t_-butylcyclohexyl system (2). It is interesting that only a single bridged ion, I, need be postulated if this mechanism is operating (Fig. 4).

In order to test the hypothesis of _cis_ protonium ion opening and to gain more information concerning hydrogen migrations in cyclohexyl systems, it is proposed that a

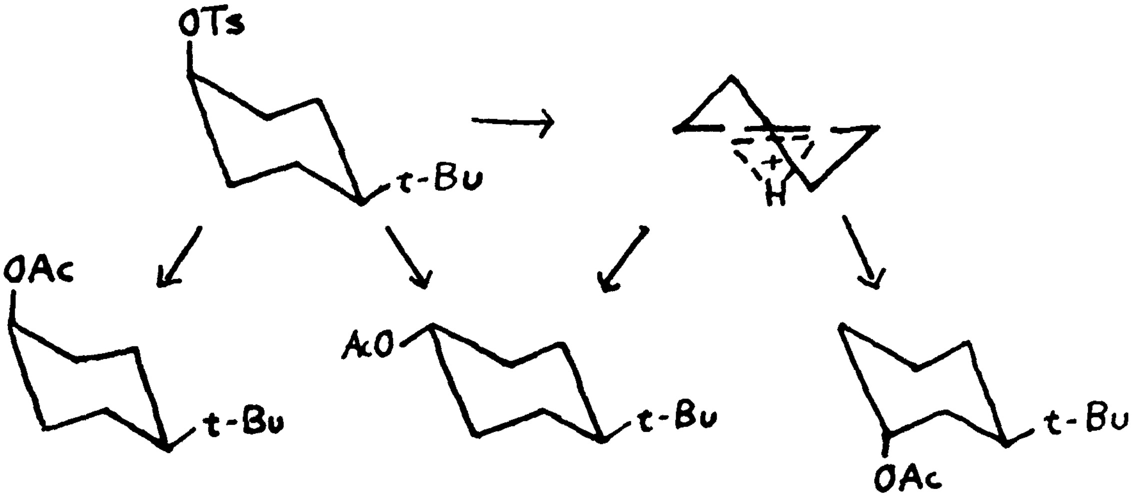

FIGURE 4

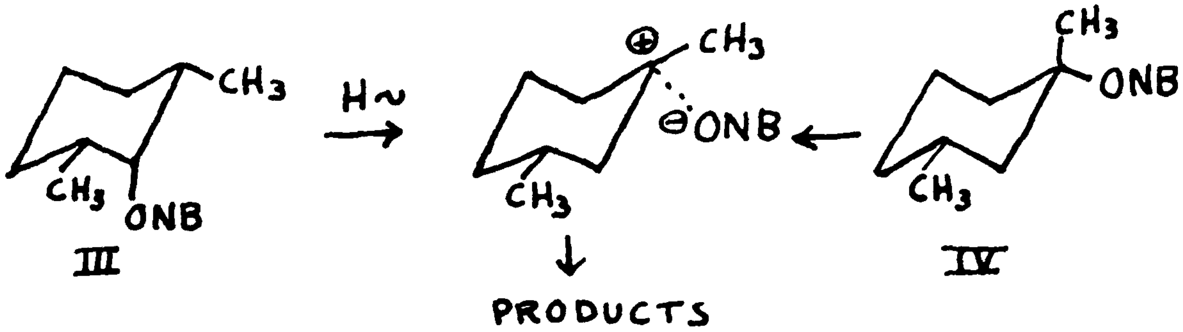

FIGURE 5

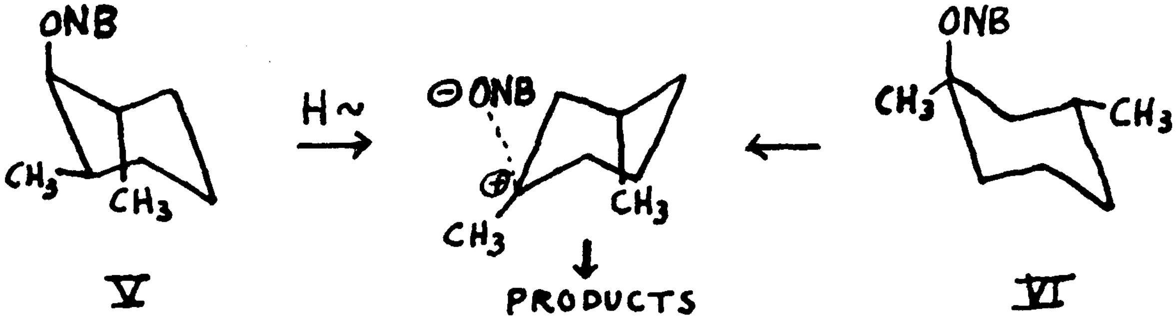

FIGURE 6

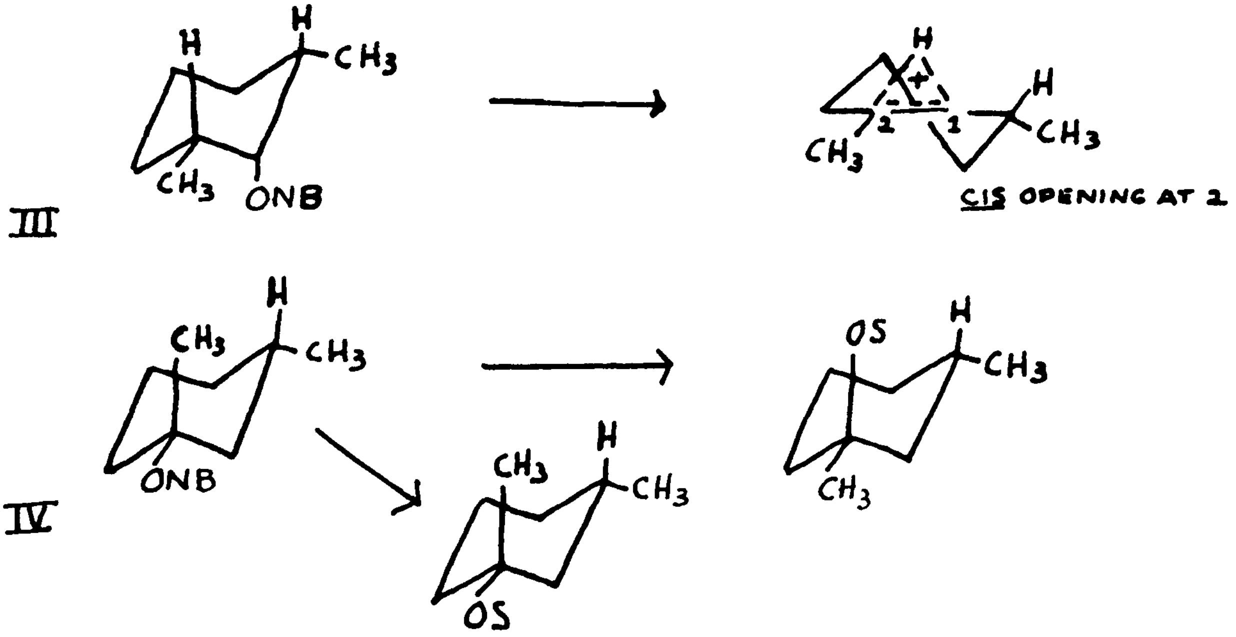

Figure 7

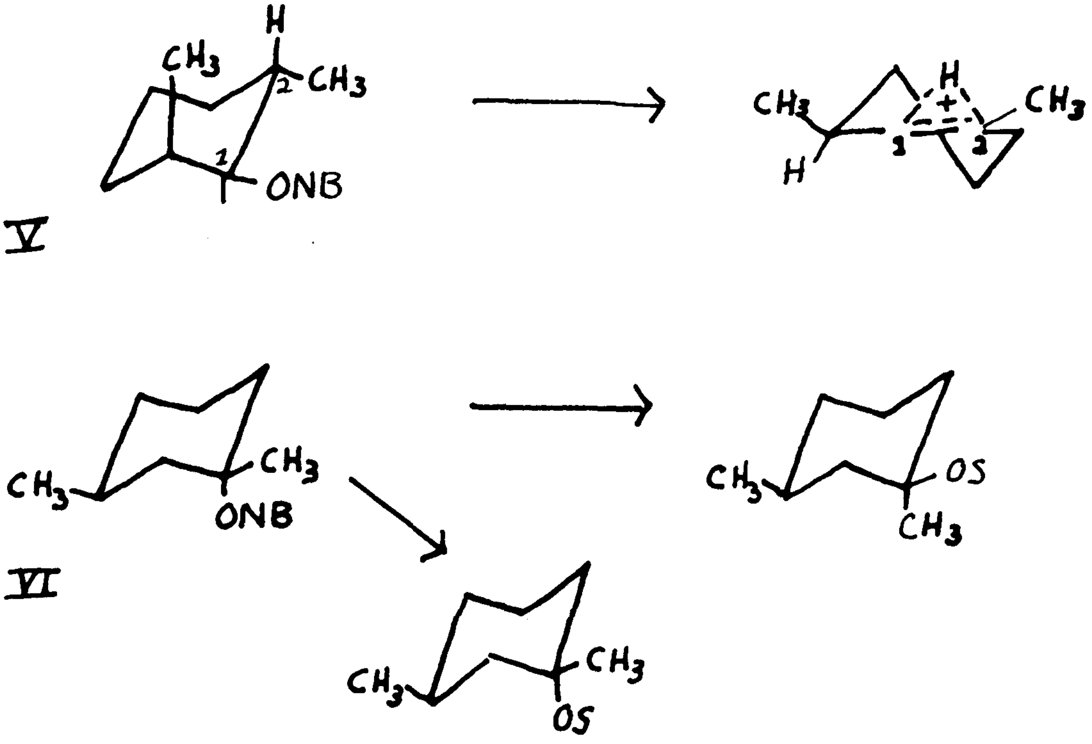

Figure 8

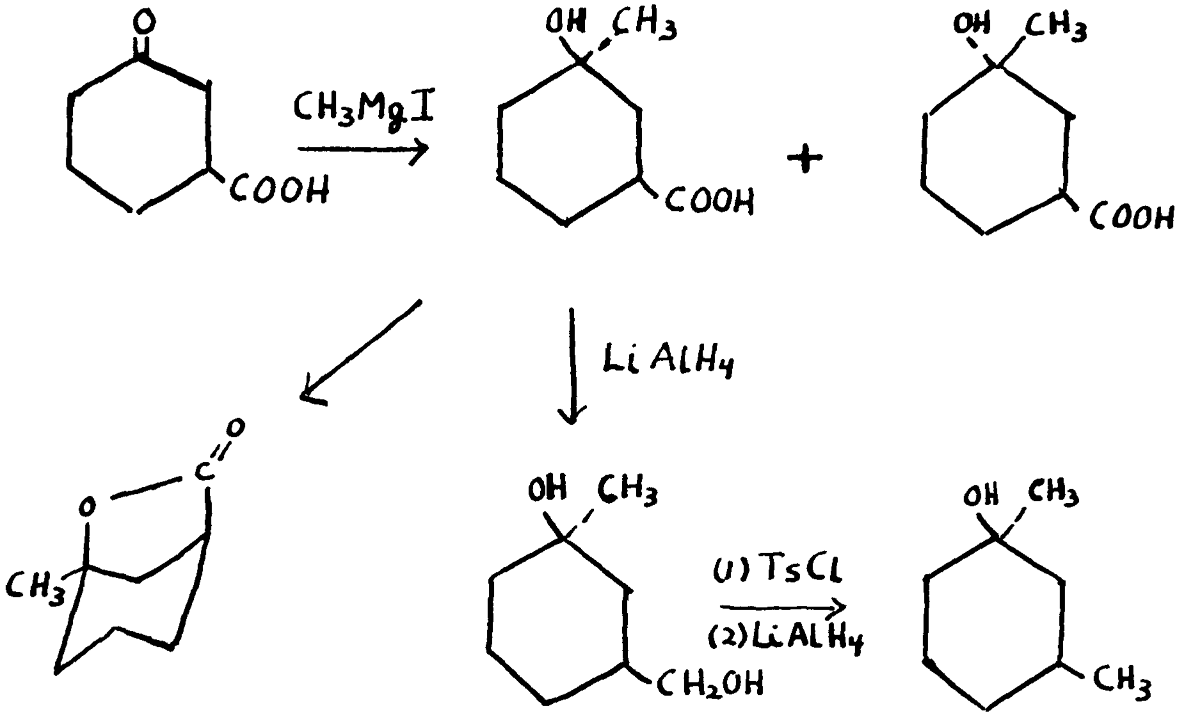
O
COOH
CH_3MgI
OH
CH_3
COOH
+
OH
CH_3
COOH
$LiAlH_4$
O
C
O
CH_3
OH
CH_3
CH_2OH
(1) TsCl
(2) $LiAlH_4$
OH
CH_3
CH_3

FIGURE 9

comparison of solvolytic products of 2α,6α-dimethylcyclohex-1α-yl (III), 1β,3α-dimethylcyclohex-1α-yl (IV), 2α,6β-dimethylcyclohex-1α-yl (V), and 1α,3α-dimethylcyclohex-1β-yl (VI) esters (*p*-nitrobenzoates, 2,4-dinitrobenzoates, etc.) be made. If a mechanism of the type depicted in Fig. 2 is operative, both III and IV would give the same 1,3-dimethylcyclohexyl products (Fig. 5). This would also be the case for V and VI (Fig. 6). A protonium intermediate is indicated if the products from III and IV or from V and VI are dissimilar. The extent of the difference of rearranged products with respect to configuration gives a measure of the amount of *cis* protonium ion opening (Figs. 7 & 8).

Configurational assignments have been made previously for the three stereoisomers of the 2,6-dimethylcyclohexyl system (4). A scheme is proposed for the assignment of configuration to the 1,3-dimethylcyclohexyl system (Fig. 9) which is based on the scheme used for assignments in the 3-methylcyclohexyl system (5 & 6).

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Proposition II.

Wittig Rearrangement at a Bridgehead.

The number of intramolecular rearrangements in which an alkyl or arylalkyl group migrates to an electron-rich carbon atom is small. The Stevens and Wittig rearrangements fit this description. In the Stevens rearrangement the migration origin is either nitrogen (ammonium halides) or sulfur (sulfonium halides), and in the Wittig rearrangement the origin is an oxygen atom (1 - 4). The groups which have been shown to migrate in one or both of these reactions include methyl, ethyl, sec-butyl, benzyl, m- and p-substituted benzyl, α-phenylethyl, phenacyl, allyl, and 3-phenylpropargyl. Both rearrangements are initiated by base (for the Stevens rearrangement, hydroxide, ethoxide, and amide, and for the Wittig rearrangement, phenyl and butyllithium, potassium amide, and propylsodium). The rearrangements may be formulated as follows (fig 1).

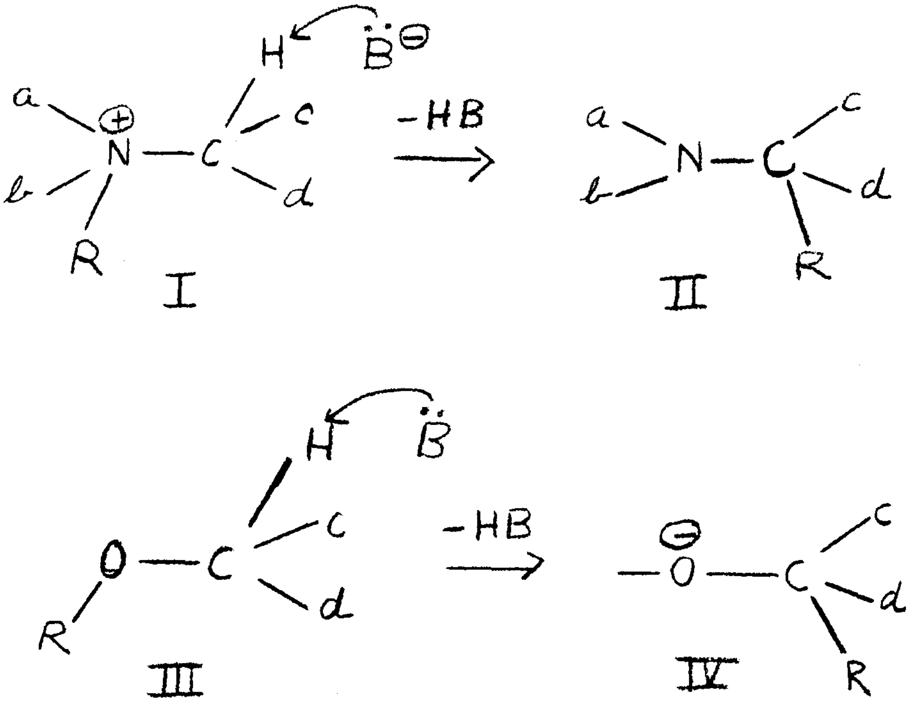

FIGURE 1

The above formulations do not specify mechanistic details; most, although not all, of the research that has been done on the electronic and stereochemical aspects of reactions of this type has involved the Stevens rearrangement. The Stevens rearrangement has been shown to be intramolecular by applying the reaction simultaneously to two different compounds (which individually react at similar rates) in the same medium and demonstrating that no interchanges of the migrating group between the two systems occurred (1b, 2). That the migrating group in the Stevens rearrangement completely retains its configuration was demonstrated using optically active α-phenylethylphenacyldimethylammonium halide (3). At least in some systems in some media a carbanion has been shown to be formed under the reaction conditions. Thus, when α,α-dideuterobenzylethyl ether was treated with propylsodium in octane, analysis of recovered starting material showed that some deuterium-hydrogen exchange had occurred (4). The rate of rearrangement of benzylphenacyldimethylammonium ion increased but approached a limit as the concentration of hydroxide ion in the medium was increased (1c). Furthermore, deeply colored solutions often develop during the reaction (1b). These facts are consistent with the reversible and non-rate determining formation of a carbanion at the migration terminus prior to the migration.

The question of whether the migrating group (R) has carbonium or carbanion character or is neutral is a subtle one. The rate-determining migration of the benzyl group in the Stevens rearrangement of the benzylphenacyldimethylammonium ion is accelerated by electron-attracting substituents in the meta and p-positions of the benzyl group ($NO_2 >>$ halogen $>$ CH_3, H $>$ OCH_3) (1b,c).

If the benzyl group were to migrate as a cation, the reverse order should be expected since the relative unimolecular rates of the corresponding benzyl halides (involving the carbonium ion intermediate, S_N1) are in the reverse order (5, 6).* Moreover, if the migration involved a free carbonium ion (i.e. not an intimate ion-pair) intermediate racemization would be expected for optically active migrating groups whereas retention has been observed (3). These data are, however, consistent with an intramolecular nucleophilic reaction of the S_Ni type involving frontside attack by the carbanionic center on the migrating carbon (6) (fig. 2, VI and VIII); consideration of the resonance structures contributing to the hybrids VI and VIII (which may be unstable transition states or intermediates) reveals that they may include some carbanionic character for the migrating group.

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*For a review of this literature see reference 7.

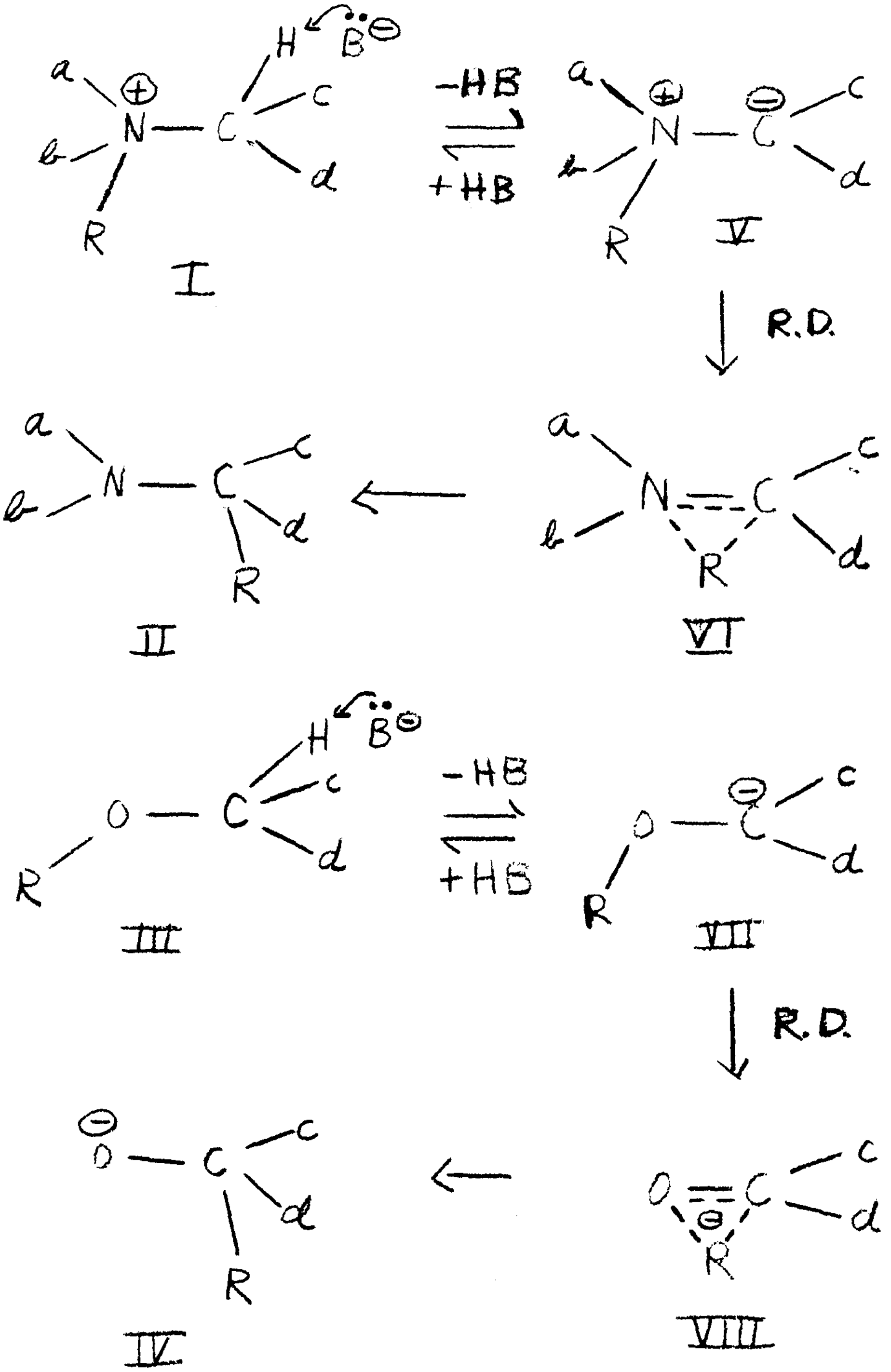

Figure 2

The data are also congruent with migration of the R group as a carbanion (1b,c) which moves from origin to terminus without racemizing. This latter possibility involves greater localization of charge than the mechanism depicted in Figure 2, and hence appears to be less favorable.

It is proposed that the suggested mechanism (fig. 2) makes this an interesting reaction to study on a bridgehead system. The essentially frontside displacement and failure to develop a substantial positive charge on the migrating center of R should allow this reaction at a bridgehead to proceed; some carbanionic character at bridgehead carbons is not unfavorable (8). In general the previously observed cases involving intramolecular rearrangements at bridgehead carbons have involved migrations to electron-deficient centers. The proposed reaction would involve migration of the bridgehead carbon to a carbanionic center.

It is proposed to study the compound 1-bicyclo[2.2.2]octyl benzyl ether in the Wittig rearrangement. The rearrangement has previously been observed with secondary alkyl groups, but no tertiary groups have been studied. Models of the proposed system reveal that the steric interference is not so great as to make the rearrangement unlikely; furthermore the β-elimination reaction which competes with the rearrangement for R =

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*A possible exception to this statement is the reaction of 4-camphylmercuric iodide with triiodide ion to give 4-iodocamphane. For a review of this literature see reference 8.

sec-butyl (4) is very unlikely here due to the difficulty of forming bridgehead double bonds. The proposed reaction conditions are phenyllithium in refluxing diethyl ether or, if higher temperatures are required, *n*-propyl sodium in refluxing di-*n*-butyl ether.

It is proposed to synthesize the 1-bicyclo[2.2.2] octyl benzyl ether from the reaction of the alkoxide of 1-bicyclo[2.2.2] octanol and benzyl chloride. The 1-bicyclo[2.2.2]octanol may be synthesized by the methods previously described (9). The product of the rearrangement, 1-bicyclo[2.2.2]octylphenyl carbinol, may be prepared by lithium aluminum hydride reduction of the corresponding ketone, which is itself prepared by the reaction of the Grignard reagent from 1-bicyclo[2.2.2]octyl chloride with benzaldehyde. This latter reaction should proceed satisfactorily since phenyl-*t*-butyl ketone may be prepared analogously in 64% yield (10), and the side reaction of β-elimination possible for the *t*-butyl case is not possible here for the reasons previously mentioned.

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Proposition III.

Conformational Analysis of the Chloro Group.

Although the free energy difference between an axial and equatorial bromine in the cyclohexyl system has been determined (1), the corresponding determination for a chloro group has not been accomplished.

The required energy differences for the chlorocyclohexyl system might be obtained from a kinetic study or equilibration experiments. In either case, a clean reaction is desired which may be followed with ease. Reactions involving bimolecular displacement of chlorine may be ruled out because competing elimination occurs. It is proposed that an E2 elimination reaction with a bulky base such as potassium t-butoxide would provide the necessary data. The rates for cis- and trans-4-t-butylcyclohexyl chloride as well as cyclohexyl chloride would be determined and dissected in the usual manner (2).

Another problem associated with the conformational analysis of the chloro group might also be examined. The equilibrium mixture of 1,2-dimethylcyclohexyl bromide in acetic acid at 25° contains 15% of the cis-1,2-dimethylcyclohexylbromide (3). It appears that bromine prefers the axial position over a methyl group (cf also reference 4). On the other hand, the infrared spectrum of 1-methylcyclohexyl chloride when compared with the spectra of steroidal chlorides indicates the chloro group to be in an equatorial position (5 & 6). By expanding the proposed study to include the 1-methyl-1-chlorocyclohexyl system more information on the relative sizes of methyl and chlorine would be obtained, and the discrepancy pointed out above would be cleared up.

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Proposition IV.

Improvement of the Low Pressure Limit Detectability of the Bayard-Alpert Ionization Vacuum Gauge.

The measurement of very low pressures is frequently accomplished with the Bayard-Alpert ionization gauge (1). The lower limit to the pressure measurable with this gauge is reached when the ion current collected becomes small enough to be masked by the residual, pressure independent photocurrent. The lower pressure limit for most gauges is in the 10^{-10} mm Hg range. With presently available vacuum system components, pressure on this order and even lower may be attained. A method for extending the low pressure limit of the Bayard-Alpert gauge is proposed.

The residual current in the Bayard-Alpert gauge is due to secondary electrons ejected from the ion collector electrode when soft x-rays impinge on it.

The cross section for secondary electron production varies as the atomic number of the target element to the fifth power (2). It is proposed that the use of a low atomic number material such as beryllium for the collector electrode will greatly reduce the low presure limit.

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Proposition V.

Secondary Emission Mass Discriminator.

A method for determining the mass of ions in a beam is proposed which is based on the transmission properties of ions through thin sheets of metal and on the dependence of secondary electron yields upon the mass of an ion impinging on a surface. The usefulness of the instrument is illustrated by its capability to resolve N_2^+ and CO^+ ions.

When ions are fired through thin metal sheets or a gas, separation according to the properties of the ions may occur. Dissociation of polyatomic ions and charge exchange may give rise to fragments of the original ion which may retain much of the original kinetic energy. For example, CO^+ dissociates when fired through a helium gas target and O^+ emerges from the far side (1). Also, although He^+ will pass through a thin sheet of aluminum, D_2^+ breaks into fragments neither of which has sufficient energy to pass through the barrier (2).

One of the present problems in mass spectroscopy is that of distinguishing between N_2^+ and CO^+ both of which have essentially the same mass. It is proposed that the thin sheet technique may be developed to permit the separation of the N_2^+ and CO^+ peaks. Presumably, if a thin metal sheet a few hundred Angstroms thick were used and a mixed beam of CO^+ and N_2^+ of high homogeneous energy impinged on the metal sheet, CO^+ would break up and O^+ would emerge from the far side. The C fragment would perhaps be trapped in the metal lattice, i.e. metal carbides would be formed. The reverse reaction is known to occur on a hot tungsten filament (3). The N_2^+ impinging on the metal sheet would be expected to dissociate and N^+ would emerge. The resulting ion beam emerging from the metal sheet would now consist of O^+ and N^+ ions of inhomogeneous energy. The masses and energies of these two ions would be sufficiently different to easily allow their separation by conventional mass spectroscopic means.

It is possible that a particular metal sheet may prefer to stop oxygen and nitrogen fragments and form oxides and nitrides. Different choices of materials for the thin sheet may alter the nature of the separation, but in general the emergent ions will have different masses and energies whether they be C^+, O^+, or N^+.

Because of weight limitations placed upon experiments to be performed in space and on planets, it may be inconvenient to analyze the emergent ion beam with a magnetic sector instrument. Furthermore, the development of new types of mass discriminating systems is of itself important. A mass discriminating device is proposed which utilizes the variation of secondary electron yield with the mass of an impinging ion. This device could be used in conjunction with the method described above for the resolution of CO and N_2 peaks.

The secondary electron yield caused by positive ions incident upon a solid surface varies as the reciprocal of the square root of the mass of the incident ion for ion energies on the order of a kilovolt (4). At higher energies the secondary electron yield varies directly with the mass of the ion (4). The yield also varies in an approximately linear manner with the energy of the incident ion (5). Also, diatomic molecules provide larger secondary electron yields than an atomic ion of the same mass (5). Organic molecules would be especially effective in causing secondary electron emission.

Developmental research would be required to determine what kind of solid surfaces would be most effective in discriminating against different masses. A wide spread in secondary electron yields is required. Perhaps materials with large secondary electron emission coefficients would be more likely to provide the required spread in yields.

An electron multiplier may be used to amplify the secondary electron yields to currents of such size as to be easily measured by counting or integrating electronics (6). Thus, the first dynode of the electron multiplier would become the source of secondary electrons due to ion bombardment. If the density of incident ions is low, the use of a multichannel pulse height analyzer and ion counting techniques on the output of the electron multiplier would yield the required mass spectrum.

One would hope that the instrument could be so developed that reasonably good resolution of adjacent masses would be accomplished. Evaluation of the instrument would be carried out by comparison of the spectra obtained with it for known gas samples. The gas sample would be ionized by use of conventional ion sources. An electric sector following the ion source produces a beam of ions having the same kinetic energy, and would be followed in turn by the secondary emission target and the electron multiplier. For application of the instrument to the separation of CO and N_2 peaks, the ion source would be followed by a mass resolving system which selects the mass 28 peak. The beam would then be accelerated to high energies, fired through the target material and strike the first dynode of the electron multiplier.

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